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THE BEHAVIOR OF PULMONARY TUBERCULOUS LESIONS

A Pathological Study

By
E. M. MEDLAR

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A Pathological Study

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FOREWORDS

FOREWORD I

Dr. Edgar M. Medlar was selected as the pathologist and director of the Hegeman Memorial Laboratory which opened upon completion in 1922 in the Sanatorium of the Metropolitan Life Insurance Company at Mount McGregor, Saratoga County, New York. The Laboratory importantly broadened the scope of the Sanatorium, which was established to care for the Company's employees, primarily those sick with tuberculosis. The Laboratory was erected and equipped at the instance of the trustees nominated and appointed in the Last Will and Testament of John R. Hegeman, a former President of the Company, with funds of the estate as specifically directed by the testator and for the objects of the Sanatorium devoted to the Company's welfare work for the benefit of the Home Office and Agency employees.

With the exception of a brief intermission, Dr. Medlar continued in that capacity until the Sanatorium and the Laboratory were closed in 1944, when the property was purchased by the state of New York to establish there one of the finest and most modern institutions for convalescent care of its veterans. From then until October 1, 1948, he continued his research, financed by the Hegeman Memorial Fund, using material from the medical examiner's office in New York City and the medical records from various hospitals.

Dr. Medlar is eminently outstanding in the field of pathology; he was honored quite recently with the award of the Trudeau Medal, the highest honor which can be bestowed by the National Tuberculosis Association. It is a pleasure to write a foreword for this monograph, for the writer has known Dr. Medlar during his whole career and was intimately associated with the founding and functioning of the Hegeman Memorial Laboratory.

This work is a summary of Dr. Medlar's experience in the study of the pathology of tuberculosis; a study which has carried him through many paths and new trails in a sincere and single-hearted effort to discover what tuberculosis is all about. This monograph summarizes his experience to date in a life which has been devoted to unraveling the secrets of the disease. Tuberculosis is still with us, although the pattern of its appearance, morbidity, and mortality has changed since 1922. Despite the splendid record of achievement in reducing the death toll from tuberculosis, the disease still ranks among the important public health problems in this country. There can be no let-up in the campaign against the disease.

The provisions of Mr. Hegeman's will are notable in performance, particularly for the selection of Dr. Medlar as the pathologist and director of the Memorial Laboratory at the Sanatorium, where he was devoted to the welfare of Metropolitan Life Insurance Company employees. As the sole surviving trustee of those who were given the responsibility of carrying out the provisions of the

will, it is gratifying to have had a part in making available sufficient of those funds to defray the cost of printing and distributing this monograph to those who are devoting their lives, or a major portion of their attention, to the study of tuberculosis.

It is my sincere hope that Dr. Medlar's observations will serve as stepping stones to the ultimate eradication of that disease.

F. H. Ecker
Honorary Chairman of the Board
Metropolitan Life Insurance Company
1 Madison Avenue
New York, New York

May 26, 1954

FOREWORD II

The peculiar and somewhat unique ways of tuberculosis enable it to retain a grip on the people which has been relaxed but slowly at some points. The usual means of transmission are well known, but prevention of this is difficult because of the insidious, subtle, and enduring character of the disease. The habits of growth and tenacity of the bacillus, especially within tissues of the body, and the mechanisms of vital resistance against the invader need further elucidation. Consideration of these features always leads to the lesion where the issue between the host and the invader is fought out. Probably no better way will be found to penetrate the secrets of the contenders than to examine the field of conflict and follow out uncovered clues. While these investigations continue, useful information, however fragmentary, must be translated into clinical practice for the benefit of patients and others who cannot await the future fruits of research.

While several generations of pathologists and clinicians have been familiar with such important phenomena as the bronchial spread of the infection through the lungs and the form of lesion acting as its source, identification of the process in the living patient by the older diagnostic procedures is crude and difficult. Roentgenography surpassed all other methods for this purpose and is now the best way of mapping lesions and tracing their evolution grossly. Even so, there are still many changes which are so fine and subtle as to elude or deceive the clinician, and the nature of the mechanisms can only be surmised or inferred.

Dr. Medlar's devotion to the experimental study of tuberculosis and to human pathology in the light of experimental findings has enabled him to accumulate a fund of knowledge which has fundamental significance and, at the same time, helps to bridge the gap between basic mechanisms and clinical manifestations. The skill, precision, and soundness of his work is reflected in the carefulness of his descriptions and the beauty of his illustrations. Speaking for the clinician, it may be said that a familiarity with this work will increase his confidence in the accuracy of inferences which he may draw from clinical data and objective findings. His practice will benefit accordingly.

It has been my privilege for a decade to be associated with the author of this monograph and to observe his work closely. Our discussions of the intricacies of tuberculosis have often led us to the borders of the known, where we could speculate on what lies beyond. Many questions have been posed, and the answers to some of them are set down in these pages. I have derived a better understanding of the essential nature of tuberculosis, especially of lesions in their early stages, and have been enabled with greater conviction to proceed with the treatment of patients in a manner calculated to avert further destructive inroads of the disease and to accomplish a lasting cure. It is a great satisfaction to know that publication of the monograph will afford similar opportunities to others.

The factual character of the observations is exceptional. One can hardly appreciate this unless he is intimately aware of the scrupulous and almost interminable work involved. A truly scientific attitude and approach have been maintained. It is notable that the dynamism of tuberculous lesions is demonstrated so clearly.

There are still some far horizons in the pathology of tuberculosis, considering the vital processes which determine its course. Investigators cannot explore these systematically without the guidance of fundamental facts such as those recorded and elucidated by the author. His work adds strength to our general defenses against a major disease which probably will be with us perpetually, at least as a potential threat.

J. Burns Amberson,
Chest Service, Bellevue Hospital
New York, New York

January 10, 1955

INTRODUCTION

"Men who have excessive faith in their theories or ideas are not only ill prepared for making discoveries; they also make very poor observations."

C. BERNARD

"Before terminating this article, I would beg the reader to remark how important are exactness and details in researches of pathological anatomy."

P. CH. LOUIS

This will be a recording in sequence of the major studies of pulmonary tuberculosis which the writer began in 1927 and has pursued without interruption through 1952. It presents the observations and the interpretations of the observations of a pathologist who has sought to understand the dynamics of tuberculous disease.

The data to be considered are so varied that the presentation is subdivided into several chapters. Some of the chapters end at a natural break in the subject matter, whereas in others an artificial break has been made for ease of presentation. It is hoped that each chapter is of sufficient brevity to permit a thoughtful reading at one sitting. However, the dissertation as a whole is the unit and each chapter should be considered as an integral part of the whole.

In several chapters the presentation of observations are interspersed with the writer's interpretations, which are intentionally somewhat provocative in nature. In Chapter X, "A Re-examination of the Problem," the writer has attempted to draw together in concise form his interpretations of the observations presented in previous chapters. It is hoped that these interpretations are stated with sufficient clarity to be understood even though the reader may heartily disagree with them. There is need for an impersonal divergence of views relative to the difficult and still unsolved problem of pulmonary tuberculosis. If the contents of this dissertation are sufficiently controversial to stimulate further effort to solve the problem, then its purpose will have been accomplished.

The writer is fully aware of the voluminous literature on pulmonary tuberculosis. However, any discussion of the views of other writers has been purposely avoided, for this presentation is not intended to be a textbook. To discuss the views of others adequately would make the text excessively long.

The writer is indebted to many individuals who have worked with him or have served as sounding-boards in the discussion of problems from time to time. The appended bibliography serves to recognize several co-workers. To all of the others to whom the writer is indebted, he wishes to express his appreciation and say a simple "Thank you all."

The writer accepts full responsibility for the contents of the text, both as to the data and to the interpretations presented. Whatever errors of fact or of interpretation may be herein are his own—albeit unwittingly made.

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CHAPTER I

STATEMENT OF THE PROBLEM

Some infections are of an explosive nature and of short duration. Either the parasite overcomes the host or the host eradicates the parasite. In infections of this nature there is a prompt sequence of morphologic events which are fairly simple and easily documented. In other infections the process is greatly prolonged and there is an ebb and flow in the course of events. Under these circumstances there develops a considerable variety of morphologic features which become difficult to document on a time-sequence schedule. The disease *tuberculosis* belongs in this category.

The main theme of the writer's investigations has been a study of pulmonary tuberculosis as this represents the major problem of this infection in man. The morphologic features of the infection merely represent the observable reactions in the tissues of the host to the presence of the multiplying parasite. They do not afford an answer to the nonobservable tissue changes which precede the observable phenomena. However, to the writer, it would seem that a more intelligent approach to an investigation of the inducers of morphologic changes would be possible once the sequence of morphologic events is established.

As this presentation is intended to record only the experiences of one student, it would seem to be both out of place and unnecessary to present an adequate review of the voluminous literature on the subject. However, before the writer began his studies he had accepted and taught certain concepts of the disease. As a background it would seem proper to present these in brief form.

Prior to the demonstration by Koch in 1882 that tuberculosis was caused by a specific microorganism, a considerable knowledge had been gained, from clinical and necropsy studies, relative to the varied manifestations of the disease. Laennec had shown that sixteen different "clinical entities" were only different manifestations of tuberculosis. Ewart had recorded a careful analysis of vomica of the lung and had noted that primary vomica at the base of the lung were so infrequent that they could be considered as nonexistent. The pattern of phthisis, a progression of the disease from the apical portions to the bases of the lung, was well known. Other features such as necrotic or caseous foci, generalized disease, involvement of bones, kidneys, meninges, and lymph nodes were also recognized.

First Parrot and later Gohn showed that in a first infection there was a "complex" which consisted of a macroscopic lesion in an organ, such as the lung, and in the lymph nodes which lay in the path of lymph drainage from the parenchymal lesion.

Baumgarten was among the first to study experimentally produced disease in animals. It was he who postulated that the reaction to the tubercle bacillus was "productive" and that the various types of cells of an organ all participated in the process. The tuberculous lesion was a new growth; a neoplasm rather than an inflammation. A zone of fibrous tissue was formed about this lesion as it grew; hence,

it was a "closed" lesion. Eventually the central portion of the lesion underwent necrosis. The "tuberculoma," which is found not infrequently in man, would be a lesion of this nature. Baumgarten observed the process of sloughing in his experimental animals; he postulated, however, that this process was of a chemical nature and was not directly related to the tuberculous process.

Koch found that, after a first inoculation of tubercle bacilli, an animal inoculated a second time several weeks later reacted in a manner which differed from the first infection. The second inoculation was promptly followed by an intense local inflammatory reaction with prompt sloughing, and the ulcerated area soon healed. This did not occur with a first inoculation. The phenomenon was interpreted as an ability of the reinfected animal to localize and heal the second infection. In this manner the bacilli of the second inoculation were discharged from the host. Subsequent studies showed, however, that the reinfected animals eventually died from a generalized infection.

Later Koch demonstrated that an acute local inflammatory reaction occurred in an infected animal if the crude products of tubercle bacilli were inoculated into the skin. This crude substance was called tuberculin and became known as Old Tuberculin. Pirquet introduced the term *allergy* to indicate that a changed condition had occurred in the tissues which enabled them to react vigorously to tuberculin. This reaction came to be regarded as an allergic response which was thought by many to have a profoundly deleterious effect upon the pathologic response in the tissues of persons who became "reinfected." This led to the postulate that a first infection with tubercle bacilli was an innocuous affair from which progressive disease did not occur. Progressive disease came to be regarded as a "post-primary" manifestation. The dividing line here was that the manifestations of the primary infection ended with the development of allergy, the ability to react to tuberculin. All manifestations of the disease after the appearance of this phenomenon came to be regarded as a reaction to reinfection. This concept led to the belief that all progressive tuberculosis in adults was caused by a "reinfection."

In the teachings in pathology, tuberculosis was included in a group of diseases which was called granulomata. A granuloma was defined as a circumscribed collection of epithelioid cells and leukocytes, chiefly lymphocytes, which resembled granulation tissue. This reaction surrounded a central point of irritation. The initial tuberculous lesion was considered to be the tubercle. A tubercle was defined as an isolated nodule or group of nodules which was composed of epithelioid cells and giant cells and which was prone to necrose and caseate. The necrosis was regarded as due to a lack of nourishment and hence was an example of ischemic necrosis; a sort of infarction. Caseation was defined as the conversion of necrotic tissue into a granular, more or less pultaceous, amorphous mass which was of a grayish or light yellowish color, resembling cheese.

Tubercle bacilli were to be found in the periphery of the necrotic area or in the adjacent living tissue. Here they were within epithelioid cells and giant cells. The presence of epithelioid tubercles and giant cells in the living tissue adjacent to a caseous focus was interpreted as a reactivation of the disease. Not uncommonly, tubercle bacilli gained access to lymphatic channels, and in this way "satellite" tubercles were formed. The necrotic lesion, if the bacilli were all disposed of, did not break down; it proceeded to inspissate, to calcify, and to organize by fibrosis. These old necrotic lesions represented healed and obsolete tuberculosis.

The necrotic or caseous focus sometimes underwent suppuration, and the suppurative process which destroyed the peripheral fibrotic capsule was ascribed to one of two causes. The first was an allergic response, an acute purulent inflammatory exudate, to the products of the tubercle bacillus, primarily tuberculin. The second was the occurrence of an acute respiratory infection in the region of the tubercle. This latter concept led to the view that progressive pulmonary tuberculosis was commonly a mixed infection. With the suppuration a bronchus was broken into, and from here on progressive pulmonary tuberculosis was an open ulcerative process with cavity formation and all of its sequelae. With a closure of the cavity, the breach in the fibrotic "capsule" was bridged by fibrotic tissue and the lesion again became sealed off.

The parenchymal component of the primary complex was regarded as relatively innocuous; however, the lymph node component was of serious import. Tubercle bacilli escaped from the necrotic lymph node, gained entrance to the major lymphatics, and gave rise to a lympho-hematogenous dissemination. This commonly occurred early in the infection and, because of this situation, tuberculosis came to be considered a generalized infection. If the lympho-hematogenous seedings were few in number, the foci became localized and often remained latent for years. The progressive disease of early and later adult life resulted from an activation of these latent post-primary lesions which occurred in childhood. This applied to renal and bone tuberculosis; moreover, the breakdown of the focal lympho-hematogenous seedings in the upper portion of the lungs initiated progressive pulmonary tuberculosis or phthisis. The disease was separated into a childhood and an adult type. The spread of the disease in the lung was regarded as an endogenous reinfection. A heavy discharge of bacilli into the blood stream from necrotic lymph nodes led to acute generalized miliary tuberculosis and to tuberculous meningitis.

It was noted that in "endogenous reinfection" there usually was no lymph node involvement such as was a common feature in a primary infection. This was attributed to the fact that the allergic state of the tissues made possible a prompt localization of the disease by blocking the lymphatics. An exogenous reinfection was considered to be rare, if not impossible.

Tuberculosis was a disease of the young and of the poor. A person who failed to develop tuberculosis by the age of thirty-five was thought to be immune to infection. Although the disease was not inherited, there was an hereditary disposition. There were tuberculous families and there was a phthisical habitus. The redhead, the diabetic, and the black-haired, blue-eyed, fair-skinned Irish were especially prone to contract the disease. Jewish people were particularly resistant to the infection, and the Negro and some primitive peoples were especially susceptible.

The above were the major concepts of tuberculosis which were in vogue prior to 1927. To the writer they did not provide a satisfactory explanation of the dynamics of the disease. Questions arose. Is the "tubercle" the initial response to the damage caused by the tubercle bacillus? If so, what morphologic changes occur in this structure and what is the time-sequence of these changes? What is the sequence of morphologic changes which precede and which follow the occurrence of necrosis and of caseation? Is the major feature of the histopathology of tuberculosis a granuloma? Is the initial tuberculous lesion in the lung one which is sealed off by a fibrotic capsule? To what extent does the infection

extend through the fibrotic capsule? Is cavity formation dependent upon a rupture of the fibrotic capsule into a bronchus? In what manner does an allergic state of the tissues alter the morphologic features of the disease? Can the variety of morphologic features found in tuberculosis be satisfactorily explained on the general nonspecific phenomenon of inflammation and repair of damaged tissue; that is, in so far as morphologic features can explain a pathologic process? Is tuberculosis usually a generalized infection almost from its inception? If so, to what extent is lymph node disease the source for the generalized dissemination? What evidence is there that latent apical pulmonary lesions are the result of a lympho-hematogenous seeding? Is all progressive pulmonary tuberculosis initiated by "endogenous reinfection"? Is there such a thing as a reinfection tuberculosis in the sense that a first infection has healed completely? If so, can the morphologic features of a progressive primary infection be clearly differentiated from those of a progressive reinfection?

The problem in tuberculosis is to obtain an understanding of the dynamics of the disease, and it seems plausible that answers to the preceding questions, and perhaps others, might aid considerably in this direction. A study of human tissues which are infected with the tubercle bacillus cannot be expected to give the answers to many of the questions. The reasons for this situation are clear. Most interpretations of the sequence of events in tuberculous infection have been based upon the study of tissues obtained from necropsies performed upon persons who have died from the infection. The morphologic features in such tissues are so variable and so complex that it is most difficult, if not impossible, to reconstruct a logical morphologic sequence because the time-sequence of events is unknown. All of the lesions are in an allergic soil. The exact date of infection is unknown, and the progress of the disease can be related only to the first definite clinical manifestation of illness. This is a most unreliable starting point. It is quite as logical to attempt to determine the dynamics of pulmonary tuberculosis from a study of lungs obtained from those who died from the infection as it would be to outline the details of a drama from witnessing only the last act.

The major problem of tuberculosis in man is the infection of the lungs, and the initiation of this infection is predominantly air-borne. Experimentally it has been shown that particles which contain tubercle bacilli must be less than 15 micra in diameter if they are to reach and be retained in the pulmonary parenchyma. Animals which inhale larger particles fail to become infected. The lesions which develop from these minute particles are of microscopic proportion at first, and the number of lesions which develop is related roughly to the number of infected particles which have been inhaled and retained. These lesions are widely distributed in the lung parenchyma, and no large pneumonic areas are found for several weeks. It seems probable that this situation pertains to the natural air-borne infection in man with the exception that the air which human beings inhale is never so heavily polluted with tubercle bacilli as is that which is used in animal experiments. If this is the way in which pulmonary tuberculosis in man

begins—and it appears reasonable to the writer that it is—then the possibility of ever determining the time-sequence of morphologic changes, and hence the dynamics of the disease, would seem to be most remote. On the other hand, a study of the time-sequence of morphologic changes in experimentally produced pulmonary tuberculosis is feasible. In the following chapter will be recorded some of the more pertinent features which were observed in an experimental study which extended over a period of fifteen years.

CHAPTER II

THE EXPERIMENTAL APPROACH

The goal of an investigation of an infectious disease should be an attempt to understand the dynamics of the disease in the natural host. A study of the morphologic features of a disease can unveil only one portion of the process, and thus has its limitations. Demonstrable changes represent only the reactions to chemical alterations in the tissues which have preceded the observable pathologic features. The nature of these chemical changes can hardly be determined on a morphologic basis. It seems reasonable to expect that a fluctuation in the chemical processes would occur during the course of an infection and that, with these changes, features in the morphologic process also might change.

In a study of the general process of inflammation and repair of damage to tissue, a change occurs in the cellular composition as one goes from the early to the completely healed stage. It seems reasonable to the writer to interpret the variability of cellular response in an infectious process as a part of the general process of inflammation and repair of damaged tissues and to regard the morphologic manifestations of an infection as nonspecific in nature. On this basis the specific differences are to be found in chemical reactions. Each type of leukocyte would seem to perform a different function, and the different types of leukocyte probably are attracted into areas of damaged tissue by the presence of chemical alterations which they are endowed functionally to meet. On the basis that a flux occurs in the chemical reactions, one can then better understand a change in the cellular contents of an inflammatory process in its different phases.

There are several natural hosts to pathogenic mycobacteria; however, in these natural hosts the types of mycobacteria are not identical. Furthermore, although there are certain morphologic features of the natural disease in the different tuberculous infections which resemble those found in man, in few lower animals is the lung the major seat of disease. It is the dynamics of the pulmonary disease in man which is of particular concern because, with an elimination of pulmonary infection, the problem of tuberculosis would vanish in large measure.

Cattle could be used in experimental studies although they are a natural host to the bovine type of bacilli. The lung is the principal seat of infection, and usually the infection is air-borne. Many of the morphologic features in bovine tuberculosis closely resemble the disease in man; however, on practical grounds, the expense of conducting any large, long-range experiments with cattle prohibits their use. Also the pattern of disease in the lungs of cattle is not that found in human lungs. The major progressive disease occurs in the caudal and dorsal rather than in the cephalic and dorsal portions of the lung.

In the use of an unnatural host, the investigator is faced with the problem of obtaining at least an analogue of all the significant features of a disease as

they occur in a natural host. In human tuberculosis the chief features are: a progressive and extensive involvement of the lungs; tubercle formation; necrotic or caseous lesions; suppuration with cavity formation; endobronchial dissemination; inspissation and calcification of necrotic lesions; scarring which results from a complete healing of parenchymal disease; and the development of an ability to react to tuberculin. Unless a way is found to produce these various features, valid objections may be raised to an application of the time-sequence of events as observed in the experimental animal to the dynamics of the disease in man.

In the search for an animal which would be a suitable host to justify an extensive experimental investigation, it was found that not all species of animals react in a similar manner to all types of tubercle bacilli which are known to be pathogenic. Moreover, it was found that the morphologic features of disease could be different in the same host if different types of bacilli were used. This perhaps is most clearly shown in the rabbit if virulent avian or virulent bovine bacilli are injected intravenously. The animals infected with the avian tubercle bacilli all die from the infection; the pulmonary lesions are inconspicuous; extensive disease develops in the liver, spleen, and bone marrow; the morphologic feature is an almost pure monocytic reaction; and necrotic lesions fail to develop. The animals infected with the bovine tubercle bacillus also all die from the infection; extensive pulmonary tuberculosis develops; although lesions develop in the spleen, liver, and bone marrow, they are not a conspicuous part of the disease; the predominant cellular type in the lesions is the neutrophil; and, at the time of death, necrotic pulmonary lesions are abundant.

After considerable study the rabbit and the bovine tubercle bacillus were chosen by the writer to carry on a thorough investigation. With this combination, an extensive pulmonary tuberculosis with necrotic lesions could always be produced regardless of the route by which the tubercle bacilli were introduced into the tissues. The most consistent results could be obtained by intravenous inoculation, and this method was used in the major experiments which will be referred to below. In all experiments, the ear vein was used as the site for inoculation. An added advantage of the intravenous inoculation of bacilli was that all portions of both lungs became involved. This proved to be important, as an ability to react to tuberculin regularly developed and, in some of the experiments, an unexpected pattern of pulmonary disease occurred which required consideration in relation to a hypersensitive state of the tissues.

Although progressive pulmonary tuberculosis, necrotic lesions, and an allergic state were easily obtained in this experimental infection, the other features commonly found in human pulmonary disease proved difficult to produce. To satisfy the investigator that all of the essential features of the human disease could be produced in the rabbit required the employment of many artifices and a pursuit of the problem for a period of fifteen years (4, 5, 9, 10, 17, 18). Of the many experiments performed, only the pertinent features of a few will be presented. No experiment contained less than 20 animals, and in some instances 50 or 100 animals were used. All of the animals were young adults of various breeds

and were nine to twelve months old. Some of the experiments were repeated to make certain that the phenomena observed were reproducible. The various organs of all animals were thoroughly examined both grossly and microscopically. Although tuberculous lesions were present in other organs, only the pulmonary lesions will be discussed.

I. VIRGIN SOIL

The Reaction to Virulent Bacilli

All of the animals to be used in an experiment were inoculated intravenously on the same date with the same amount of a fine suspension of tubercle bacilli which was devoid of clumps. In the basic experiment, 0.05 mg. of tubercle bacilli, wet weight, was the dosage used. Sacrifice of pairs of animals was begun at the end of twenty-four hours and was continued daily thereafter until the first death from the disease occurred. Thereafter the animals were examined promptly as they died. The earliest death occurred within six weeks, and the last survivor died within three months of inoculation. Invariably the longer the animal lived, the greater was the amount of pulmonary disease. It was evident that there were some, although perhaps slight, differences in the native resistance in this heterogeneous group of animals.

The lesions became visible at approximately the tenth day, at which time minute whitish foci were found fairly evenly distributed throughout both lungs. As time passed, all of the lesions increased in size; many coalesced; and eventually the major portion of the lung parenchyma was occupied by nodules of varying sizes. In the late stages, when death occurred, the lesions were firm and on section many showed a central portion which was of a light yellowish-gray color. Macroscopically, there was no evidence of softening of the lesions or of cavity formation, even in the animals which survived the longest.

A microscopic study of the disease process showed a progressive inflammatory process without tubercle or giant-cell formation and without any evidence of an attempt to wall off the foci by fibrotic tissue.

At forty-eight hours the minute foci consisted of a focal area of alveolar walls which were broadened by congestion and an accumulation of a mixture of monocytes and neutrophils. The adjacent alveolar spaces contained a few neutrophils. Tubercle bacilli were most difficult to find but were present. *At five days* the microscopic focus was considerably larger, due to an accumulation of leukocytes. The predominant cellular type was the neutrophil. The alveolar spaces immediately adjacent to the damaged alveolar walls were completely filled with leukocytes, and in the surrounding alveolar spaces there were a variable number of these cells. The lesion had already become an open area of lobular pneumonia. Bacilli were more easily found but were not numerous.

By the end of the second week (Plate I, figure 1) the areas of lobular pneumonia were considerably larger, and original foci which happened to lie close together had coalesced. The area of the initial focus was now considerably larger than at its beginning and in the central portion there was a firmly packed mass of neutrophils, and large numbers of tubercle bacilli were present. In the periphery of

the lesion, however, the cellular exudate consisted of a mixture of neutrophils and monocytes. In this peripheral area bacilli were present in small numbers and usually were phagocyted by either neutrophils or monocytes.

The core or central portion of the lesion had the structure of an early abscess; however, there was no evidence of necrosis. If an initial lesion happened to be adjacent to a bronchus, the bronchial wall had become involved in the developing abscess and there sometimes was a local loss of the bronchial epithelium. In such bronchi there were a few neutrophils, an occasional monocyte, and a few phagocyted tubercle bacilli. The beginning of infected bronchial exudate was present which later became a potent source for endobronchial dissemination. Another source for endobronchial dissemination was the spilling over of the inflammatory exudate into minute bronchial branches which were directly in association with the enlarging lobular pneumonic lesion. An occasional focus was present in the extreme periphery of the pulmonary parenchyma. Such foci sometimes involved the pleura and, even at two weeks, minute fibrotic pleural adhesions were found on occasion.

By the end of the fourth week, a profound change had occurred in the central portion of the enlarging pneumonic lesion. Necrosis was well on its way. The process began at the periphery of the area which was to necrose and proceeded inward. The evidence for this was that identifiable leukocytes were easily found in the central portion and were not found in the necrotic periphery in many of the lesions. At this time tubercle bacilli within the necrosing zone were less numerous than at two weeks. There was no evidence of a zone of fibrotic tissue between the necrosing zone and the remainder of the lesion.

By the time the animals began to die (Plate I, figure 2), the necrotic foci were larger and more numerous; and the longer the animal lived, the more extensive was the necrosis of the pneumonic lesions. After recognizable cellular elements disappeared in the zone of necrosis, tubercle bacilli, although present, were difficult to find. In the areas which had not necrosed, however, bacilli were fairly easily found although they were not in the tremendous numbers which were present in the core of the early abscess at two weeks.

The sequence of events just related was readily reproducible. The disease was a progressive inflammatory process with little evidence of repair and with no histologic tubercle formation. The experiment afforded an excellent opportunity to determine the time-sequence of events which were related to necrosis.

The initial focus passed through the early stages of abscess formation and then, instead of proceeding to the stage of liquefaction and sloughing, the area merely necrosed; this occurred in both the lung parenchyma and in the inflammatory exudate. As tubercle bacilli were much more numerous in the area before than after necrosis, it seems doubtful that the necrosis could be related directly to the growth of bacilli. Rather there occurred an extensive lysis of bacilli with the development of necrosis, and it would seem that the process was directly related to the destruction of bacilli. If that is the case, then perhaps the coagulation necrosis represents a side effect of the process which is required to lyse considerable numbers of tubercle bacilli. With death of the neutrophils

their proteolytic enzymes apparently ceased to function and perhaps that is the reason for the failure of the tuberculous abscess to continue promptly to the natural process of liquefaction and sloughing.

These animals began to react to tuberculin in the third week after inoculation, and within a week or two it was unusual to have an animal which was not a reactor. It is during this period that large numbers of bacilli were being destroyed, and it seems plausible that the development of the allergic state may be related in some way to the products of the disintegrating bacilli. A reasonable postulate is that the allergic state develops along with, but may not be the cause of, the process of necrosis.

The Effect of Dosage

Considerable emphasis has been placed upon the effect of the initial dosage of bacilli in human tuberculosis. In the experiments described above, the dosage used was 0.05 mg. of bacilli. To determine the effect of dosage, two different types of experiment were done. In one, a dosage of 1 mg., wet weight, and, in the other, 0.001 mg. was employed. Otherwise the experiments were identical to the experiments already described.

The animals in which 1 mg. of bacilli was used all showed a tremendous number of individual foci. These foci progressed in a manner similar to that already described. All of the animals were dead within six weeks, and the pneumonic disease (Plate I, figure 3) was so extensive that little uninvolved parenchyma remained. A few foci had undergone complete necrosis, but the large majority showed only the beginning of the necrotic process. Bacilli were present in large numbers in the pre-necrotic lesions and were scarce in the completely necrotic areas. From the extensive pneumonic process it seems probable that death in most instances was caused by anoxia.

The animals in which 0.001 mg. of bacilli was used showed only a few widely scattered foci. The manner of early progression of these lesions was the same as that already described. All animals died in four to six months. At the time of death there were widely scattered focal lesions (Plate I, figure 4) which varied in size from a couple of millimeters up to 2 cm. in diameter. The largest foci were firm and of a light yellowish-gray color without macroscopic evidence of liquefaction or of cavity formation. Microscopic study showed that they were caused in large part by endobronchial dissemination, as marked ulcerative bronchial disease was present, and they all contained large areas of complete necrosis. The smaller foci seemed to be endobronchial disseminations of fairly recent origin, as many were foci of lobular pneumonia without evidence of necrosis.

Bacilli were difficult to find in the wholly necrotic foci; they were more easily found, although not in large numbers, in the smaller non-necrotic lesions. There was little evidence of any healing of the lesions, although there were focal areas of calcification in some of the large necrotic foci. In some areas, especially in the ulcerative bronchial lesions which were continuous with large necrotic areas, the necrotic debris was heavily infiltrated with neutrophils, and in some of these

areas bacilli were fairly numerous. The principal features of the pathology in these animals were: large areas of complete necrosis; marked ulcerative endobronchial disease; focal areas of calcification in the large necrotic foci; and considerable endobronchial dissemination. These features would seem to be related to the longer period of survival because of the small dosage of bacilli.

Reaction to Bacilli of Low Pathogenicity

In these experiments BCG was used; this strain of bovine bacilli has lost its ability to cause progressive disease if kept under properly controlled conditions. Intravenous inoculation of 10 to 20 mg., wet weight, of bacilli was the method used. In this manner a tremendous number of minute foci were produced in the lungs. These foci were first visible at the end of three weeks, and a week later chest roentgenograms showed the typical pattern of miliary tuberculosis. The inflammatory response was at its height (Plate II, figure 5) at this time and thereafter receded, so that at six months, with occasional exceptions, the lungs presented a normal macroscopic appearance. None of the animals died from the infection even though many were allowed to live for two years.

Microscopic study of the lesions showed a rather slow tempo in development of the inflammatory response. *In the first week*, although the focal lesions were of microscopic proportions, the composition of the cellular elements did not vary significantly from that found in infection with virulent bacilli. Thereafter, although considerably larger focal areas of lobular pneumonia developed, the cellular response consisted predominantly of a mixture of monocytes and lymphocytes. There was no evidence of necrosis. Tubercle bacilli were more easily found at the end of a month than in the earlier lesions; they were widely dispersed and they were never present in large numbers. From this it would seem that the bacilli had succeeded in multiplying to some extent during the first few weeks.

At three months many of the animals showed relatively few well-localized lesions (Plate II, figure 6). The major portion of the lung parenchyma presented a normal appearance. Many of the remaining foci consisted of a collection of monocytes and, in a few, an occasional giant cell was seen. A few of the focal lesions consisted of collections of lymphocytes. *At six months* the only microscopic evidence of disease consisted of a few widely scattered small parenchymal scars and small collections of lymphocytes. Tubercle bacilli were not found in the lesions at three months or later. However, it seems probable that a few bacilli were present in the histologic tubercles which were present at three months.

Of particular interest in this series of experiments was one rabbit which was sacrificed eighteen months after infection. The lungs of this animal contained a considerable number of firm widely scattered nodules which were 1 to 2 mm. in diameter. Microscopic study of many lesions showed a considerable variation in the morphologic picture. There were typical histologic tubercles with and without giant cells. Peripherally, these lesions showed a thin fibrotic zone and a "collar" of lymphocytes. There were wholly necrotic lesions which were

surrounded by a thin zone of fibrous tissue and contained a variable number of lymphocytes in their periphery. Some of these necrotic foci showed considerable calcification and others did not. Fibrotic scars with and without lymphocytic infiltration were present, and obstructive emphysema was associated with some of the scars. In one non-necrotic tubercle, a colony of acid-fast bacilli was found and this colony was largely surrounded by neutrophils. This was the only lesion in which tubercle bacilli were found.

With few exceptions, the animals in this series of experiments showed an ability to react to tuberculin when tested after two months. Rarely was there any evidence of a necrotic lesion. From this it would seem that the development of an allergic state is neither dependent upon nor the cause of the phenomenon of necrosis.

It was found in these experiments that, although large numbers of focal pneumonic lesions developed, these in large measure resolved completely. Small numbers of scattered histologic tubercles, analogous to similar lesions in man, were sometimes found after the major pneumonic process had resolved. These lesions later disappeared and would seem to be the areas in which microscopic scars were found. On rare occasions an animal showed a few scattered abscesses which necrosed and later became calcified and organized without any further progression of the disease.

Usually the animals in these experiments became reactors to tuberculin. It was evident that there was some difference in the native ability in a heterogeneous group of animals to deal with an infection with tubercle bacilli of low pathogenicity. It was in this delicate balance between the native resistance of the host and the pathogenicity of the tubercle bacilli that the histologic tubercle and the small abscesses which underwent necrosis, encapsulation, and calcification were found.

II. REACTION TO VIRULENT BACILLI IN AN ALLERGIC SOIL

In the preceding experiments it was found that an allergic state developed in an infection which the rabbits commonly completely healed. This permitted a study of the reaction to virulent bacilli introduced after a complete eradication of a previous infection had occurred. In such an experiment, remnants of a previous infection would not confuse the picture.

Groups of animals which had been inoculated intravenously with 10 mg., wet weight, of BCG six months and one year previously were reinfected intravenously with 0.05 mg., wet weight, of virulent bacilli; this was the same dosage that was employed in the first experiments commented upon.

In these experiments an occasional animal died in the second week after reinfection. Such animals showed an almost complete acute pneumonic consolidation (Plate III, figure 8) of both lungs.

Microscopic study showed that the inflammatory reaction consisted largely of a mixture of neutrophils, monocytes, and lymphocytes in varying proportions in different areas. A few minute abscesses were found, and an occasional minute necrotic focus was present. Acid-fast bacilli were present in small numbers and

were widely distributed. It appeared that these animals died from anoxia rather than from tuberculosis.

A few animals were sacrificed at one month. The lungs showed generalized miliary tuberculosis. Microscopic study showed a few widely scattered small necrotic foci. At this time the inflammatory reaction consisted almost entirely of a variable mixture of monocytes and lymphocytes. In a few areas, poorly formed histologic tubercles and occasional giant cells were seen. The focal pneumonic areas were quite sharply localized, and there were considerable areas of normal lung parenchyma.

No more animals were sacrificed, and the disease process was allowed to run its natural course. The animals began to die at the eighth month (Plate III, figure 9), and the last survivor died at the eighteenth month after reinfection. In all of these animals the extent of disease was much greater in the kidneys than in the lungs. It seems probable that death was due to the extensive renal tuberculosis rather than to the pulmonary disease.

The condition found in the lungs was not anticipated. Bilaterally, the original disease had completely healed in the cephalic and ventral portions of the lungs, except for some endobronchial disseminations from the cavities; however, in the caudal and dorsal portions there was a bilateral chronic cavitary tuberculosis. The tuberculous cavities showed a peripheral fibrotic zone and an inner necrotic zone which was heavily infiltrated with neutrophils. Tubercle bacilli were present in considerable numbers in the inner zone of the cavity wall in some sections and were difficult to find in others. The cavities varied considerably in size, and this was taken to indicate that necrotic pneumonic areas of different sizes had formed prior to liquefaction and sloughing. The endobronchial disseminations which were present in other portions of the lungs showed a variable morphology. Some were necrotic with a periphery of fibrotic tissue and some were recent non-necrotic areas of lobular pneumonia. No large endobronchial disseminations were observed. Bacilli were not numerous in any of these disseminated lesions; they were found in some sections and not in others. A restudy of the lesions present at one month after reinfection failed to reveal any significant differences between the foci which were present in the area in which the cavitary disease was later found and those which were present in other areas in which the disease had healed.

It became evident from these experiments that the inflammatory response was much more vigorous and prompt in the animals in an allergic soil than in virgin soil. Also it was evident that the changes in the pulmonary pathology led to a very different pattern of disease and that, if the early inflammatory response was not overwhelming, the animals did quite well, in so far as the pulmonary involvement was concerned. It seemed impossible to explain purely on an allergic basis, however, the fact that in one portion of the lung the disease underwent complete healing and in another portion a chronic progressive cavitary tuberculosis developed.

The chronic pulmonary disease in these animals resembled in many respects that which is found in man. The principal differences were that the cavities developed in the wrong end of the lung and that extensive endobronchial dis-

surrounded by a thin zone of fibrous tissue and contained a variable number of lymphocytes in their periphery. Some of these necrotic foci showed considerable calcification and others did not. Fibrotic scars with and without lymphocytic infiltration were present, and obstructive emphysema was associated with some of the scars. In one non-necrotic tubercle, a colony of acid-fast bacilli was found and this colony was largely surrounded by neutrophils. This was the only lesion in which tubercle bacilli were found.

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The chronic pulmonary disease in these animals resembled in many respects that which is found in man. The principal differences were that the cavities developed in the wrong end of the lung and that extensive endobronchial dis-

seminations had not developed. It is not possible to say that extensive dissemination would not have occurred later had the animals not succumbed to the extensive bilateral renal tuberculosis. The writer believes that, except for the fact that the cavitary lesions were always bilateral, the pattern of pulmonary disease in these rabbits represents an analogue to the disease in man, and this pattern of disease in man is generally regarded as a "so-called" reinfection disease. It was obtained in the rabbit as a result of reinfection in allergic soil and it was reproducible. The question immediately arose whether a similar pattern of disease could be obtained from a first infection in nonallergic soil.

III. AN ATTEMPT TO PRODUCE A CHRONIC CAVITARY PULMONARY TUBERCULOSIS IN A FIRST INFECTION

It was found that, no matter how small a dosage of fully virulent bacilli was used, a progressive pulmonary lesion developed wherever tubercle bacilli happened to lodge in the lungs. Although cavitary disease (Plate II, figure 7) could be produced, if an animal survived a long time, a pattern similar to that observed in reinfected animals could not be consistently produced.

At the time of these experiments, there was available in the laboratory a culture of bovine tubercle bacilli which was considered to have a moderate degree of virulence. An intravenous inoculation of 0.05 mg., wet weight, of this strain of bacilli caused a slowly progressive disease throughout the lungs, and the animals all died in approximately one year. A group of normal young adult rabbits was given an intravenous inoculation of 0.0001 mg., wet weight, of this strain. With this dosage a few widely scattered foci were produced, and animals sacrificed six months (Plate III, figure 10) after inoculation showed a few progressive lesions with necrotic centers only in the dorsal and caudal portions of the lungs. The remainder of the group of animals were kept in order that the disease process could proceed through its natural evolution.

Two years after inoculation, one (Plate IV, figure 11) of the animals died. The lungs showed a few cavitary lesions in both lungs in the caudal and dorsal portions, and on one side the entire cephalic lobe and a part of the ventral portion of the lung was the seat of necrotic tuberculous pneumonia. A few smaller endobronchial disseminations were present in both lungs. The remaining animals were sacrificed a few months later, and bilateral cavitary disease was present in each in the caudal and dorsal portions of the lungs. The number of cavities varied from one to a few in each lung, and there were a few small endobronchial disseminations which were considered to be of fairly recent origin.

From the results of this experiment, it is evident that a pattern of disease similar to that obtained in the experiments on reinfection is obtainable in a first infection. The important points appear to be that a proper balance must be obtained in a first infection between the native resistance of the host, the dosage, and the virulence of the infectious agent and that a considerable lapse of time is required to allow the development of the disease.

One puzzling feature was the failure of original foci to progress in other areas of the lungs. That other foci were present was deduced from the presence of

small histologic tubercles and collections of lymphocytes. It would seem most unlikely that focal deposits of bacilli other than in the dorsal and caudal portions of the lungs would fail to occur in a group of animals which had been infected by intravenous inoculation.

IV. CAN POSTURE BE A FACTOR?

The pattern of bilateral chronic cavitary pulmonary tuberculosis in rabbits was obtained in virgin soil and in allergic soil by intravenous inoculation into ear veins and was related to the higher portions of the lungs, the caudal and dorsal areas. One may consider these areas as the more vulnerable portions with the rabbit in a normal position. A quite similar pattern was found in natural air-borne infection in cattle (22). However, in cattle, frequently only one lung was involved. This would suggest that the route of infection was not as important as the fact that both animals were quadrupeds. In man, a biped, chronic cavitary tuberculosis, an air-borne infection, develops primarily in the cephalic and dorsal portions of pulmonary lobes; frequently the disease is unilateral. To complete the series of investigations, it was decided to explore the possibility of changing the site of progressive disease from the caudal to the cephalic portion of the lung by forcing the rabbit to maintain the posture of a biped.

In the pursuit of this problem (19), the numerous difficulties encountered in the attempt to get normal animals to live for a considerable period in an upright position will not be discussed. In the early attempts, some of the animals died without evident cause of death; chylous ascites, torsion and gangrene of the gut, and frequent aspiration pneumonias were encountered. Eventually it was found that the best procedure to follow was to place a firm binder about the belly combined with a jacket about the chest. A ring was placed in the upper posterior portion of the chest jacket, and a wire from an overhead trolley line was snapped into the ring in the jacket. With proper adjustment the rabbit could be maintained in an erect position and could jump about on the floor for exercise. Food and water were so located that they were easily accessible. The majority of the animals survived this arrangement for weeks, provided they were not required to remain in the upright position more than eight or ten hours a day. Each morning the animals were harnessed up and placed in the erect position, and each evening they were unharnessed and permitted to return to their normal posture.

A group of 12 normal young adult rabbits were conditioned to this procedure for two weeks, by which time 2 had died from pneumonia. The remainder were inoculated intravenously with 0.0001 mg. of tubercle bacilli of moderate virulence, the strain which was used in the previous experiment. Six of the animals survived for five months, and then all were sacrificed within a month.

Each (Plate IV, figure 12) of the sacrificed animals showed a bilateral progressive, fairly well localized tuberculosis in the cephalic portion of the lung. In 4 of the 6 animals, one or more much smaller necrotic lesions were also present in the caudal and dorsal portions of the lung. Apparently eight hours a day in an erect position greatly retarded but did not completely prevent some progres-

sion of the lesions in the dorsal and caudal regions. The remainder of the lung tissue showed only a few widely scattered collections of lymphocytes. These were interpreted as the remnants of other focal lesions which had occurred as a part of the intravenous seeding. Perhaps with a continuation of the experiment, cavitary disease might have developed in the cephalic portion of the lung. Be that as it may, the most progressive disease had been shifted to the cephalic portion of the lung; this situation had not been found in various other experiments. It seems plausible that, through posture, certain portions of the lung become more vulnerable to tuberculous infection and that this may be of considerable significance in man in the early stage of the disease. No explanation of the phenomenon is offered, for it would be only theoretical speculation.

V. NOTES ON OTHER EXPERIMENTS

Early in the studies, a group of 24 pure-bred young Ayrshire steers were used to test out the efficacy of vaccination with BCG. All of the animals failed to react to tuberculin before the experiment was begun. Twelve animals were used as controls, and 12 were given a subcutaneous injection of 10 mg. of BCG in the groin. The two groups of animals were kept in separate enclosures. All of the vaccinated animals were reactors to tuberculin when tested six months after vaccination, and none of the control animals were reactors. Two vaccinated animals were sacrificed at this time, and the only evidence of tuberculosis was a well-circumscribed, somewhat inspissated necrotic lesion at the site of inoculation. All of the steers were then given an intravenous inoculation of 1 mg., wet weight, of virulent bovine bacilli.

Within six weeks of the challenge inoculation, 3 animals had died from fulminating generalized tuberculosis, 2 in the control group and one in the vaccinated group. No more animals died over the ensuing nine months, at which time all were sacrificed. In every animal, both control and vaccinated, well-localized and relatively small tuberculous lesions were present in both lungs and in spleen, liver, and kidneys. Most of the vaccinated animals showed a well-encapsulated necrotic focus at the site of inoculation with BCG, but in 3 only a scar was present in this region. Microscopic study of the tuberculous lesions in the various organs showed no clear-cut differences between the vaccinated and nonvaccinated groups. One would anticipate that the vaccinated animals might localize the tuberculous disease; however, one would not anticipate that normal animals would do the same. This experiment clearly demonstrates the value of using many animals in an experiment.

During the course of the experiments with rabbits it was noted that small tuberculous foci developed in the appendix and in the region of the ileocecal valve. This is the site of the greatest aggregations of lymphoid tissue in the gut of the rabbit. This intestinal infection was found to occur only in rabbits which had ulcerative tuberculous lesions in the lungs and, hence, followed the swallowing of infected sputum.

To study the development of tuberculosis in normal rabbits infected by the oral route, 20 mg. of virulent bovine bacilli were placed in a small gelatin cap-

sule and the capsule was then sealed by dipping into melted gelatin. The capsule was pushed into the esophagus a sufficient distance so that regurgitation and chewing of the capsule could not occur. It was found that infection of the intestine did not occur regularly with the swallowing of a single capsule. To assure infection in every animal, a capsule was given once a week for six weeks. All of the animals then developed a progressive tuberculosis of the appendix and in the region of the ileocecal valve. The early lesions were usually few in number and were of minute size. Within a year all of the animals had died from extensive pulmonary tuberculosis. The early pulmonary tuberculous lesions were few in number, small in size, and widely scattered in both lungs.

All of our studies in reinfection after vaccination had been done by the use of intravenous inoculation of bacilli. This is an unnatural procedure and introduces far more tubercle bacilli than would reach the lungs through either aerogenous or ingestion routes of infection. It was believed that perhaps the efficacy of BCG had not been given a fair trial.

As the number of initial lesions which occurred in the appendix in the previous experiment were few in number and of small size, an experiment was set up in which a group of normal rabbits were given an intravenous injection of 20 mg. of BCG and six months later were fed capsules which contained 20 mg. of virulent bovine tubercle bacilli once a week for six weeks. The results (30) of this experiment showed that half of the animals failed to develop demonstrable intestinal lesions. In the other animals, small focal lesions developed which in the majority remained fairly well localized and which progressed extensively in some. Ten per cent of the group which showed intestinal lesions eventually died from extensive pulmonary tuberculosis; only 5 per cent of the whole group developed progressive pulmonary disease. This experiment represents a fair test for the efficacy of BCG vaccination and probably indicates the best which can be expected from prophylactic vaccination.

A considerable study of tuberculosis in normal and vaccinated guinea pigs was carried out. This animal was not suitable for these studies for the reason that necrotic lesions similar to those produced in rabbits and commonly found in man were not found. Rather, the lesions were of the abscess type which did not proceed to complete necrosis.

GENERAL COMMENT

The purpose of all of this experimental program was to find out whether it was possible to obtain in an unnatural host the significant morphologic features of pulmonary tuberculosis which were known to occur in man. Analogues of the essential features of human disease were obtained through the use of various artifices. The time-sequence of events in the various processes was determined. The conditions under which the various features could be produced were determined, and under proper conditions the lesions were reproducible. The important lesions were histologic tubercle formation, necrosis, and cavity formation with endobronchial dissemination.

The histologic tubercle was not found to be the initial response in the lungs to either a primary or reinfection disease. Rather it appeared at a later date; it was not of serious import and it healed by scar formation.

Necrosis was preceded by the formation of the early phases of an abscess in which the neutrophil was the predominant cellular component; the necrotic process first became evident at the periphery of an area and evidently was not induced because of ischemia. It appeared to be a process connected with the lysis of tubercle bacilli, and the necrosis of the area appeared to represent a side effect of the process. The phenomenon of necrosis seemed to be unavoidable if considerable numbers of bacilli in a localized area were to be lysed. The disposal of the necrotic lesion was difficult. The lesion was an open area of lobular pneumonia prior to necrosis, and a peripheral fibrotic capsule was not laid down until after a necrotic area had become well defined.

The liquefaction and sloughing (suppuration) of a necrotic lesion were considerably delayed. In this process neutrophils reappeared and seemed to be an essential feature. With liquefaction, the necrotic debris with its bacillary content was drained off through the connecting bronchial tree and, in this fashion, tuberculous cavity formation came into being. Until the parenchymal framework within the necrotic lesion became thoroughly disintegrated, large areas could not slough and macroscopic evidence of cavity formation was absent. Local areas did liquefy and spill into connecting bronchi. These areas were focal ulcerations. They represented the microscopic beginning of cavity formation. Endobronchial disseminations occurred from microscopic focal ulcerations as well as from macroscopic cavities.

The establishment of an allergic state in the tissues proved in general to be beneficial. The predominant feature in allergic soil was that the inflammatory response was much more prompt and vigorous than in a virgin soil. On occasion this response was overwhelming and led to a disastrous result. The process of necrosis was not related directly to the effect of an allergic state; however, necrosis did occur more promptly in an allergic soil than in a virgin soil. The same concept seems reasonable in an interpretation of liquefaction and sloughing, although this phenomenon always occurred in a soil that was allergic.

These are the essential features of the dynamics of the experimentally produced tuberculosis. The time-sequence of events was found to be predictable. These features are not obtainable if investigations are limited to a morphologic study of the disease in man. Although the concepts presented have been obtained through the use of artifices in experimentally produced tuberculosis, it seems reasonable that they can be applied to an interpretation of the disease as it is found in man. In the presentation of data obtained from a study of human tissues, these concepts will be applied.

PLATES I-IV

PLATE I*

FIG. 1. (× 15) The focal areas of open lobular pneumonia at two weeks after intravenous inoculation of 0.05 mg., wet weight, of virulent bovine tubercle bacilli in a normal rabbit. The deep blue central portions are composed of tightly packed neutrophils. Tubercle bacilli are present in large numbers in this portion of the lesion. Peripherally bacilli are also present in small numbers. There is no evidence of necrosis. No "epithelioid" tubercles or giant cells are to be found. There is no evidence of fibrotic encapsulation of the focal lobular pneumonic foci.

FIG. 2. (× 2) Lung of a rabbit in the same experiment as figure 1. The animal died in six weeks. The red-staining foci are areas of necrotic lobular tuberculous pneumonia. The blue-staining areas are those in which viable inflammatory cells are present. These cells are a variable mixture of neutrophils and monocytes (epithelioid cells). Phagocytosed bacilli are found more easily in these areas than in the necrotic areas. Numerous bronchi are involved and the larger lesions are due in large part to endobronchial dissemination. There is no evidence of either liquefaction or fibrotic encapsulation of the necrotic areas. No "epithelioid" tubercles or giant cells are present.

An occasional animal of a group might live for three months. The only major difference in the lungs of such rabbits is that larger and more numerous necrotic lesions are present.

FIG. 3. (× 15) From lung of a normal rabbit which was given an intravenous inoculation of 1.0 mg., wet weight, of virulent bovine tubercle bacilli. Death occurred in one month. Illustration is typical of all lung tissue. The wholly red lesions are completely necrotic. Other lesions show a reddish periphery and a bluish central portion. These are in an earlier phase of necrosis. Otherwise the pathologic process is not essentially different from that shown in figures 1 and 2. Note the involvement of the large bronchus in the upper portion of the illustration and the exudate present in its lumen. The blue color in the necrotic area adjacent to the bronchus is due to a heavy infiltration of neutrophils. All animals were dead in six weeks.

FIG. 4. (× 2) Normal rabbits received an intravenous inoculation of 0.001 mg., wet weight, of virulent bovine tubercle bacilli. Illustration is from lung of a rabbit which died in four months. Note the variations in size of the red necrotic pneumonic lesion. The largest necrotic lesion represents the involvement of a considerable area of lung parenchyma through endobronchial dissemination. Large areas of the lung parenchyma were not involved in the tuberculous disease.

A few "epithelioid" tubercles and giant cells are present. There is little production of a fibrotic "capsule" about any of the necrotic lesions. The dark blue spots within the large necrotic lesion are focal depositions of calcium salts.

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* The photographs from which all of the illustrations have been made were done by Mr. William P. Ficklin. I wish to express my deep appreciation of the meticulous care with which the photographs were prepared.

Ektochrome color films were used.

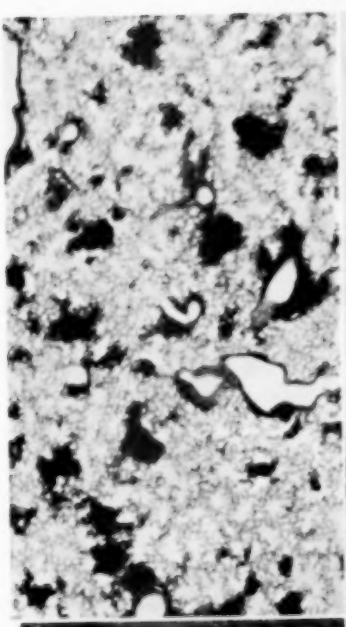


Fig. 1

Fig. 2

Fig. 3

Fig. 4

PLATE I

PLATE II

FIG. 5. (× 15) Illustration shows the inflammatory response at its height after intravenous inoculation of 10 mg., wet weight, of BCG. The rabbit was sacrificed one month after inoculation. Both lungs were thickly studded with small lesions. The small areas of open lobular pneumonia are composed almost wholly of monocytes (epithelioid cells) and lymphocytes. In a few of the lesions there is a minute area of necrosis. Chest roentgenograms of rabbits at this stage show the picture of miliary tuberculosis.

FIG. 6. (× 15) Section of lung from a rabbit in the same group as that shown in figure 5. Animal was sacrificed at four months. The lesions in the illustration are typical "epithelioid" tubercles in some of which giant cells are present. At this stage these foci are scattered throughout both lungs and in large part the lung parenchyma has returned to a normal state. A few months later only an occasional animal will show any macroscopic evidence of pulmonary lesions. However, microscopic study will reveal a few small parenchymal scars.

FIG. 7. (× 3) Section from caudal portion of lung from a normal rabbit which died one year after it was fed 25 mg., wet weight, of virulent bovine tubercle bacilli once a week for six weeks. Note the cavity formation in the upper right-hand corner. The bronchus leading to the cavity is in the central portion extending diagonally upward and shows an open communication. The blue color in the lesions below the cavity and in the extreme left is due to heavy infiltration of necrotic lesions with neutrophils. There are some small foci which show epithelioid tubercles and giant cells. Note the fibrotic capsule of the cavitating lesions and the fibrotic pleural adhesions in the lower right-hand quadrant.

Lesions of this type begin as microscopic lympho-hematogenous seedings which are always bilateral, are usually few in number, and are haphazardly distributed in both lungs. The lesion illustrated happened by chance to have located in the dorsal and caudal portions of the lung. The pulmonary lesions are a part of a generalized dissemination as tuberculous lesions are always found in various organs.

It takes many months for cavities to develop. Before necrosis the neutrophil is the chief cellular component. This illustration shows an invasion of neutrophils long after a necrotic lesion has formed. Cavity formation results from a liquefaction and sloughing of an area of necrotic tuberculous pneumonia. However, endobronchial disseminations commonly occur from liquefaction and sloughing of focal areas of a necrotic lesion. At this stage there is no macroscopic evidence of cavity formation.

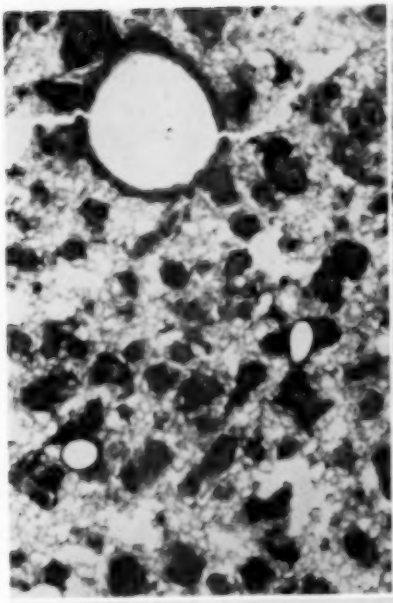


Fig. 5

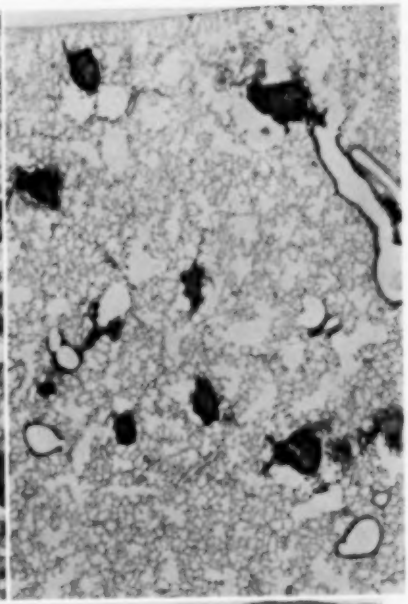


Fig. 6

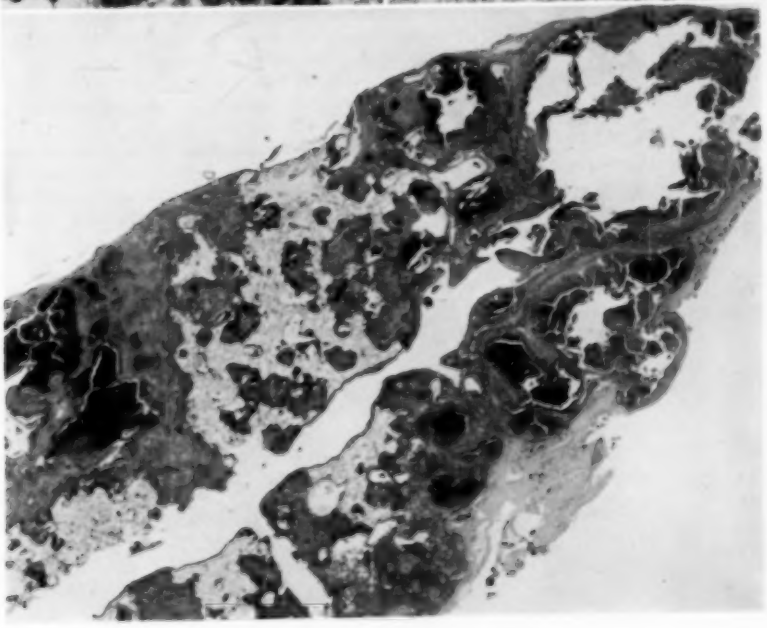


Fig. 7

PLATE II

PLATE III

FIG. 8. (× 15) Section from the lung of a vaccinated (BCG) rabbit which died ten days after an intravenous inoculation of 0.05 mg., wet weight, of virulent bovine tubercle bacilli. The animals used in this experiment had been given an intravenous inoculation of 10 mg., wet weight, of BCG nine months previous to reinfection. They reacted to intradermal injection of tuberculin. The prompt and extensive development of lobular pneumonia is out of all proportion to the numbers of bacilli that can be demonstrated and is in marked contrast to the first infection with either virulent bovine bacilli or BCG. A few small red foci indicate that already some necrosis of lesions has occurred. However, the necrosis is of minimal extent and does not become greater. One never finds any evidence of necrosis as soon as this after a first infection. Only an occasional animal dies at this stage. Gradually all of the lesions are resolved except in the dorsal and caudal portions of the lung.

FIG. 9. (× 1.5) Section of lung of rabbit which died ten months after reinfection with virulent tubercle bacilli. Animal is from same group as that shown in figure 8. The tuberculous disease has progressed in the caudal tip of the lung through local endobronchial dissemination, and the large necrotic lesions have gone on to liquefaction and cavity formation. The minute foci in the right half of the illustration probably represent the residual of small foci which had undergone necrosis and had progressed no further.

The animals in these experiments all had extensive bilateral renal tuberculosis, and it seems probable that they died because of renal insufficiency rather than from the pulmonary disease.

FIG. 10. (× 2) Section of lung of a normal rabbit which was sacrificed six months after an intravenous inoculation of 0.0001 mg., wet weight, of bovine tubercle bacilli of "moderate" virulence. Note the five lesions with necrotic (red) areas in the dorsal and caudal portions of the lobe. Note also the several minute blue spots in other portions of the lung. These are lesions which have failed to progress.

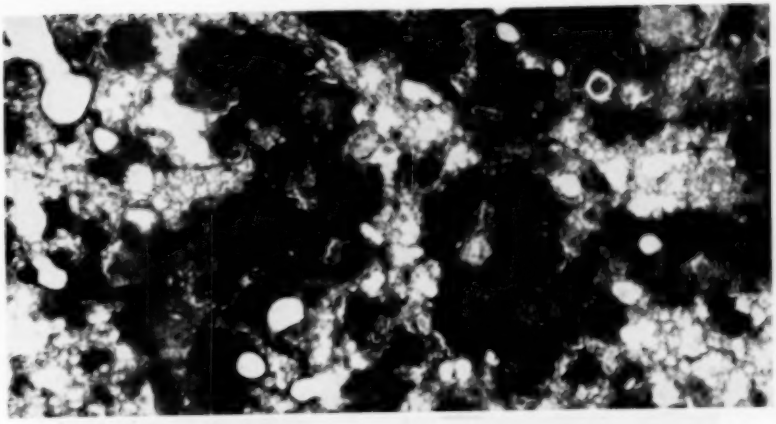


FIG. 8

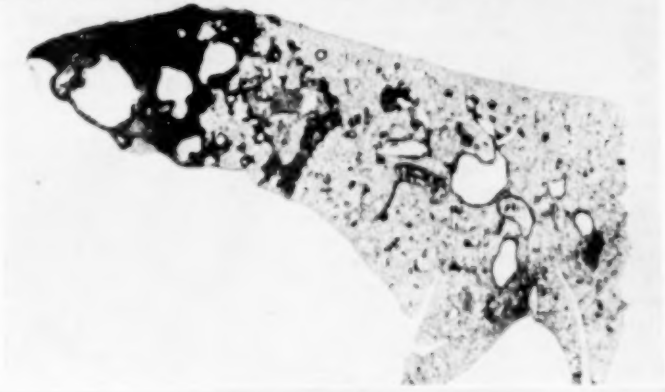


FIG. 9

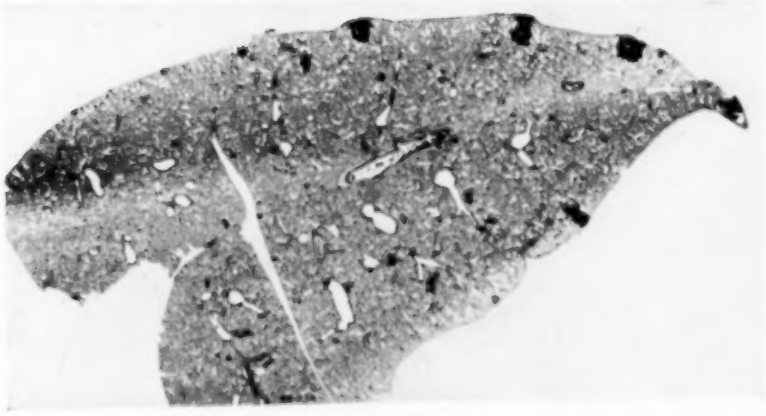


FIG. 10

PLATE III

PLATE IV

FIG. 11. (× 1.5) Section from the lung of a rabbit in the same experiment as that in figure 10. This rabbit died two years after the intravenous inoculation was given. Note the two tuberculous cavities in the caudal tip (the highest portion of the lung in the illustration) and the necrotic tuberculous lobar pneumonia of the cephalic portion of the lung. Apparently the material sloughed out of one or another of the cavities and was dispersed into the lower (cephalic portion) part of the lung. In this fashion a necrotic tuberculous pneumonia came into being. Note the few minute foci in the lung between the cephalic and caudal portions. The larger of these probably are small endobronchial dispersions. Three cavities but no large areas of necrotic pneumonia were present in the opposite lung.

All of the animals in this group were sacrificed at a later date. Each showed one or more cavities in the dorsal and caudal end of the lungs only. Both lungs presented a similar picture except that the number of cavities were not equal.

FIG. 12. (× 1.5) Section of lung of normal rabbit which was forced to stand on its hind feet eight to ten hours daily for four months after it was given the same intravenous inoculation of bovine tubercle bacilli as was used in the experiment illustrated in figures 10 and 11. Note that the progressive disease with necrotic foci is most marked in the cephalic portion of the lung (highest part of lung in illustration). Note also the two small lesions at the extreme caudal end of the lung. Eight hours a day in an upright position decreased but did not eliminate the progression of disease which was evident in the rabbit in normal position. Note also the absence of any progressive lesions between the caudal and cephalic portions. The red areas in the mid-lung field are blood vessels filled with blood. Each lung showed a similar picture. All animals in the experiment showed a similar condition when they were sacrificed at the end of six months.

Fig. 11

Fig. 12

PLATE IV

CHAPTER III

NECROPSY STUDIES OF HUMAN PULMONARY TUBERCULOSIS

After the experimental studies reported in the previous chapter had been completed, an opportunity became available to devote all of the writer's time to an investigation of the various morphologic features of tuberculosis in man. During the previous seventeen years a study of this kind purposely was postponed. It seemed advisable to wait until it could be shown that all essential tuberculous lesions known to occur in man were reproducible in an experimental animal. In the study of the disease in man, the data which had been collected from animal experimentation were found to be most useful, particularly the time-sequence of morphologic changes. This approach to the study of human tuberculosis may be unacceptable to many; however, to the writer, it is a procedure greatly to be preferred.

The data which will be discussed in this chapter were obtained from the following sources:

1. Fresh tissues from 1,332 cases of sudden and unexpected death became available through the courtesy of the medical examiner's office at Bellevue Hospital, New York City. A complete necropsy was performed in only approximately 20 per cent of the cases which came under the jurisdiction of the medical examiner's office, and the primary concern in performing a necropsy was to establish the cause of death. The writer was not responsible for the performance of the necropsies, but the tissues became available for study as soon as the medical examiner had completed his investigation. The lungs, all lymph nodes within the chest and abdominal cavity, the liver, spleen, and kidneys were all thoroughly searched for evidence of tuberculosis. Reliance was placed upon the presence of necrotic or calcified lesions as acceptable evidence of tuberculous infection; however, the writer was particularly eager to find small local macroscopic lesions in the lungs in a non-necrotic state which might represent an early phase of the disease. As the technique which was employed has been detailed elsewhere (41), it will not be described here. The examination of the thoracic and abdominal viscera was tedious and so time-consuming that only approximately one-third of the available necropsy material could be used. The cases were examined without reference to the findings of the medical examiner and may be regarded as an unselected sample, in so far as tuberculous infection is concerned, from cases of sudden and unexpected death. The study was pursued until 1,000 cases with macroscopic evidence of tuberculous infection had been obtained. More than two and one-half years were required to collect the data.

2. A careful search was made of more than 17,000 necropsy records in three large municipal and four large voluntary general hospitals located in metropolitan New York for recorded evidence of tuberculous disease in the lungs. Such records are not considered by the writer to represent a reliable source for determining the incidence of tuberculous infection; they are a fairly reliable source, however, for the description of unhealed tuberculosis which has progressed to a greater or lesser extent.

3. Fresh tissues from 100 consecutive necropsies on patients who died from tuberculosis were studied in an attempt to determine the incidence of primary and of reinfection progressive pulmonary tuberculosis. These cases came in large part from the Chest Service of Bellevue Hospital.

PRESENTATION AND DISCUSSION OF DATA FROM CASES OF SUDDEN AND UNEXPECTED DEATH

A summary of the data obtained from the study of the cases of sudden and unexpected death may be seen in table 1.

There were 290 cases in which no definite evidence of tuberculosis was found.

TABLE 1

DATA ON EVIDENCE OF TUBERCULOSIS

Medical Examiners' Cases—Sudden and Unexpected Deaths

Evidence Based upon Finding of Necrotic or Calcified Lesions

Nature of Tuberculous Lesions	Number of Cases	Distribution of Cases According to Age				
		3 months to 9 years	10 to 19	20 to 39	40 to 59	60+
Total cases	1,332	43	64	348	568	309
No calcified or necrotic lesion found	290	43	45	94	115	35
Examination unsatisfactory	42					
Necrotic or calcified lesions found	1,000	—	19	254	453	274
Single Primary Complex						
Total cases	418	—	15	106	193	104
Calcified lesions	362	—	9	76	174	103
Necrotic lesions	56	—	6	30	19	1
Multiple Primary Complex						
Total cases	123	—	—	30	52	41
Calcified lesions	102	—	—	14	48	40
Necrotic lesions	21	—	—	16	4	1
Incomplete Primary Complex						
Total cases	204	—	4	55	85	60
Nodes—no parenchymal	107	—	1	28	47	31
Parenchymal—no nodes	97	—	3	27	38	29
No Pulmonary Focus—Necrotic or Calcified Mesenteric Lymph Node Present						
Total	40	—	—	15	19	6
Pulmonary Tuberculosis of Minimal Extent or Greater						
Total cases	215	—	—	48	104	63
Minimal	104	—	—	25	46	33
Advanced: cavity absent	50	—	—	10	25	15
Advanced: cavity present	61	—	—	13	33	15

Although persons less than twenty years of age made up less than one-tenth of the cases examined, they comprised nearly one-quarter of the group in which evidence of tuberculosis was lacking. Some of the adults of this group showed small pulmonary scars; however, small scars alone were not considered to be sufficient proof that a tuberculous infection had occurred. Tuberculosis is by no means the only infection which can leave small pulmonary scars.

There were 42 cases in which a satisfactory examination was not possible. These cases included instances of lobar pneumonia in the stage of gray hepatization, extensive pneumonoconiosis, or extensive neoplastic growths in the lungs. In all, there were 332 cases in which post-mortem examination either failed to reveal convincing evidence of tuberculous infection or technically was unsatisfactory. The remaining 1,000 cases will be discussed in some detail.

Primary Complexes

In 785 cases in which acceptable evidence of a tuberculous infection was found, the lesions were too small for the persons to be considered as having clinically recognizable tuberculosis and, in most instances, were so tiny that the lesions would not be recognizable in roentgenograms of the chest. The remaining 215 patients had had tuberculous disease of the lung of minimal or greater extent. It is possible that some of the minute lesions were those of histoplasmosis; however, this disease is rarely encountered in the region of metropolitan New York City. Single pulmonary primary complexes were found in 418 cases (58 per cent); multiple complexes in 123 cases (16 per cent); and incomplete complexes in 204 (26 per cent).

One-seventh of the complete primary complexes were found to be necrotic and were regarded as infections of fairly recent origin. The incidence of these was approximately twice as frequent in persons less than forty as in those more than forty years of age. One case of particular interest in this group was that of a twenty-five-year-old aviator who was in a German prisoner-of-war camp for two years. There were five small necrotic primary complexes, one in each pulmonary lobe.

The remaining six-sevenths of the complete primary complexes were in a completely calcified state and were regarded as healed tuberculous lesions. Many of these undoubtedly were of long duration, for not infrequently bone formation (Plate V, figure 13) about the calcified area was found on microscopic examination. In approximately one-third of the cases, multiple complexes were found. One-fifth of these cases were from persons less than forty years of age, and in four-fifths the persons had been more than forty years of age at the time of death.

The group of incomplete primary complexes included cases in which either a parenchymal or a lymph node lesion was not found on macroscopic examination. It seems probable that in these cases no visible recognizable lesion was left in one component of the complex in the process of healing. On occasion, microscopic study of hilar lymph nodes reveals a minute scar which probably represents a healed non-necrotic tuberculous lesion. It seems probable that, in in-

complete primary complexes, microscopic scars in either the lung parenchyma or lymph node would represent the macroscopically unrecognized component, at least in the majority of cases.

There were 40 cases in which necrotic mesenteric lymph nodes were found in the absence of other demonstrable tuberculous lesions in either the abdominal or thoracic viscera. In most instances the lymph nodes were wholly calcified. These were considered to be primary infections derived from ingestion of bacilli. It is of interest that in these cases there was an intestinal primary infection without evidence of disease in any other organ. On the other hand, there were 15 cases of calcified mesenteric lymph nodes and progressive pulmonary tuberculosis. In these cases it seems reasonable to postulate that the pulmonary disease was an air-borne reinfection.

Distribution of the Parenchymal Component of Complete Primary Complexes

The small necrotic or calcified parenchymal focus was found in all portions of the lung. There were 100 cases of a single calcified primary complex in which the parenchymal lesion had a diameter of 2 or more mm. When these parenchymal lesions were plotted on a roentgenogram of a normal chest (41), the resulting pattern resembled the scatter of bird-shot on a paper target. One might anticipate such an even distribution from the inhalation of minute air-borne particles. A similar pattern was obtained in the plotting of small necrotic lesions and of multiple calcified foci.

In 464 cases of calcified primary complexes, there were 845 calcified parenchymal foci. Only one-eighth of these lesions were found in the apical and posterior portions of posterior segments of upper lobes, in the superior segment of lower lobes, or in the superior portion of the right middle lobe. To the writer these regions in the human lungs may be regarded as the more vulnerable portions, just as the dorsal and caudal portions of the rabbit lung were found to be the more vulnerable portions in the experimental studies. These vulnerable areas would seem to contain more than one-eighth of the lung volume and, consequently, calcified primary foci were found less often in these areas than one would anticipate. On the other hand, it is evident that in some instances tubercle bacilli may lodge in a vulnerable area and induce only a minute localized lesion which heals completely.

Usually the parenchymal lesions were found within 1 cm. of the pleura in the collapsed lung. A good many were approximately 1 mm. in diameter and occasionally were not recognized on a first examination. The lesions which lay deeper in the lung tissue often were difficult to find. This is well illustrated by a Negro lad, nineteen years of age, in whom three lymph nodes adjacent to the right upper lobe bronchus contained easily demonstrable necrotic foci. After prolonged search, a 3 mm. necrotic focus was found in the small amount of parenchyma between bronchi within 2 cm. of the involved hilar lymph nodes.

The Lymph Node in Primary Infections

In the past it has been stressed that tuberculosis of hilar lymph nodes in primary infections is a common source from which generalized disease or even progressive pulmonary disease develops. This dictum is based on the study of persons who have died from tuberculosis and in whom extensive tuberculous involvement of hilar lymph nodes is found. Disseminated disease in association with extensive hilar lymph node tuberculosis is a particularly common coincidence in infants. The group of cases under discussion would seem to afford an opportunity to determine a possible causal relationship between the two phenomena.

The group of complete and incomplete primary complexes made up 78 per cent of all of the persons with evidence of tuberculous infection, and in these persons there was no evidence of progressive tuberculous disease. They represent tuberculous infections of fairly recent origin (Plate V, figure 14) as well as of ancient origin (Plate V, figure 15).

In a group of 200 persons, each with a single complete pulmonary primary complex in which a single calcified parenchymal focus was present, 4 per cent showed calcified or densely fibrotic foci in the spleen or liver or both. In this group it would be reasonable to assume that the slight hematogenous dissemination had arisen from the pulmonary focus rather than from the lymph node component, for it would be most unusual for only a single pulmonary lesion to develop in a lympho-hematogenous dissemination. In the remaining 341 persons with complete primary complexes, multiple pulmonary foci were present and a small percentage of these also showed old foci in the spleen or liver. In this group it might be assumed that some of the pulmonary foci were of lympho-hematogenous origin. The writer does not agree with such an assumption, however, for this would predicate that in a high percentage of cases the bacilli were all filtered out in the lungs, an unlikely occurrence. In the 688 persons with lymph node involvement and without progressive pulmonary disease, there was no evidence to support the concept that post-primary, latent lympho-hematogenous apical seedings could be a common source for progressive pulmonary disease.

That a lympho-hematogenous dissemination may occur on occasion was indicated in one case which was not included in the group under discussion. In this person there was a rather large mass of necrotic nodes with large calcific areas in the mediastinum, and multiple minute fibrotic or calcific foci were scattered throughout both lungs as well as in the spleen, liver, and kidneys.

It may be that in cases of progressive disease with extensive hilar lymph node involvement a lympho-hematogenous dissemination is more common than would be indicated in the necropsy cases under discussion. However, this would be rather difficult to prove. In the writer's experience, if such dissemination did occur commonly, it would be manifested as a generalized miliary tuberculosis, which usually would terminate in death.

The writer has seen one instance in a seventy-year-old man in whom a necrotic lymph node eroded a branch of the pulmonary artery, causing generalized miliary tuberculosis. The most instructive feature of this case was that the portion of lung which was supplied by the eroded arterial branch was much more heavily seeded with miliary lesions than the remainder of the lung tissue. Nevertheless, a sufficient number of bacilli passed through this portion of the lung to make possible the development of a generalized hematogenous disease. Usually it is not possible to demonstrate the exact location from which hematogenous seedings occur. This would seem to indicate that these sites are usually of microscopic proportions.

Extent of Involvement of Lymph Nodes in Cases of Insignificant Disease

Among the 785 cases of primary complexes without evidence of significant progression of the disease, macroscopic evidence of lymph node lesions was found in 688 (87 per cent). The involved nodes varied in number from one to several. In 200 cases (26 per cent) they were easily found by inspection and palpation. In the remainder, in order to find the lesions, it was necessary to cut the lymph nodes into thin slices. Not infrequently, after an hour or more had been devoted to a slicing of all observable nodes, the only evidence of tuberculosis to be found was confined to a single lymph node which contained either a minute necrotic focus or a spicule of calcification.

The search for evidence of lymph node involvement was the most tedious and time-consuming part of the study. Even in the cases in which easily demonstrable lesions were found in lymph nodes in the direct line of drainage of a single pulmonary focus, it was necessary to section thoroughly all other lymph nodes to make certain that other evidence of tuberculosis could not be found. This is well illustrated by the case of the adult with generalized miliary tuberculosis which was discussed above.

The occurrence of a large necrotic lymph node which had eroded a branch of the pulmonary artery seemed to indicate that the case was one of progressive primary tuberculosis. After prolonged search, however, a single complete minute calcified primary complex was found in the lower lobe of the opposite lung. On a pathogenetic basis the case then appeared to be one of reinfection tuberculosis with a reinfection complex. In a study such as the one under discussion, it is evident that minute details and a thorough search must not be neglected.

It appears that there is a great variation in the extent of lymph node involvement in primary tuberculous infection. These tissues were all obtained from adults; however, if the ancient calcified lesions represent a primary infection acquired in childhood, then even in children an extensive lymph node involvement sometimes does not occur. It is also evident that extensive lymph node involvement can frequently end in complete calcification without any erosion of bronchial walls. That calcified nodes or, perhaps more likely, necrotic nodes with large areas of calcification may erode a bronchus is well known; however, this is an uncommon occurrence.

Comment on Lymph Node Involvement in Tuberculosis

With the difficulties encountered in the macroscopic demonstration of tuberculous involvement of lymph nodes, the reason is apparent for the infrequent evidence of lymph node involvement in chest roentgenograms. This pertains to progressive primary tuberculosis in young adults and also to reinfection tuberculosis in older adults, for the calcific remnants of a healed primary tuberculosis are commonly too tiny to be detected in a chest roentgenogram.

It seems probable that nothing has caused greater confusion in the clinical understanding of tuberculosis than the teaching relative to the sinister effect of lymph node infection. It is unfortunate that the findings in necropsies on persons, particularly in children, who have died from tuberculosis have been generalized to cover all tuberculous infections.

The findings discussed above are consistent with morphologic data collected on persons who died from tuberculosis and indicate that lymph nodes commonly are involved by a tuberculous process which usually undergoes necrosis, as does the parenchymal pulmonary focus. This is the feature which differentiates tuberculosis from most other pulmonary infections and which makes the disease chronic and unpredictable. Even under these circumstances, the evidence indicates that the vast majority of lymph node lesions are rather innocuous.

Evidence is lacking that the disease commonly becomes a generalized one from a primary infection or that the tuberculous lymph node is the source from which either a progressive pulmonary disease or a progressive disease in other organs has its origin. The lymph nodes in pneumococcal pneumonia usually are markedly enlarged, and yet it is not held that pneumococcemia or meningitis is caused by lymph node involvement. In pneumonoconiosis the hilar lymph nodes commonly are markedly affected; yet in most instances there is little evidence that the foreign particles get beyond the lymph node barrier.

Lymph nodes serve as filters and commonly this filter system is effective in limiting a greater dissemination of bacteria or other particulate matter. The evidence presented above indicates that the dissemination of tubercle bacilli is markedly limited and that lymph nodes play a role in this limitation. The remarkable feature in tuberculosis is that, despite the frequent presence of necrotic foci in lymph nodes, the filter apparatus succeeds remarkably well in limiting the infection.

Evidence of Reinfection

It has been commonly held that a reinfection in tuberculosis is a rarity or, in other words, that a new air-borne infection is far less frequent than a flare-up of an unhealed disease already present. The group of cases under discussion affords an excellent opportunity to investigate this problem, for the primary lesions were in large measure minute and were in a calcified state.

In assessing the evidence for reinfection, the writer considered small calcified foci as old healed lesions and small necrotic foci as lesions of a more recent origin. In the study of experimentally produced tuberculosis, the necrotic lesion

was found to be present within six weeks in a first infection and to occur somewhat earlier in a reinfection. Consequently, the necrotic foci in the human cases are at least several months old, for in the majority of instances they showed an organizing fibrotic periphery.

Included in the group of 464 patients who had complete calcified pulmonary primary complexes, there were 45 patients (10 per cent) with small necrotic lesions which would suggest reinfection tuberculosis. The necrotic foci varied from one to nine (Plate V, figure 16) in number and, if multiple, were widely scattered. Ten of the cases of reinfection showed a necrotic focus in the lymph nodes which lay in the line of drainage of the necrotic parenchymal focus. This was an entirely unexpected finding, as it is commonly held that lymph nodes in reinfection do not show macroscopic evidence of tuberculosis.

In many cases, especially in those of multiple primary complexes, there were more calcified foci than could be related directly to the primary infection. Although it is not possible to prove that these extra calcified foci represent healed reinfections, it is possible that many of them may have been so. In situations such as this, the inability to establish time relations in the disease in man makes it impossible to reach a conclusion in the matter. Neither can one be certain that some of the multiple complexes are not healed reinfection complexes. It has been shown, however, that multiple primary complexes which were all in a necrotic state do occur, and it seems reasonable to assume that such lesions could completely heal with only calcific remnants to indicate the condition. From these remarks it should be evident that, even in the cases in which the disease has healed completely, it is not possible in many instances to be certain of the sequence of events. The important point is that reinfections do occur.

General Comment

The group of 785 cases which have formed the basis for the data and comment so far have included minutiae which required meticulous attention to minor details in order to serve as evidence. This part of the study may seem to be of no significance, especially to the clinician or surgeon. It must constantly be borne in mind, however, that tuberculous infection has its beginning in a minute microscopic focus which may or may not become of serious import to the infected person. As this group comprised approximately two-thirds of the necropsies, it appears that an infection with tubercle bacilli is not a serious affair in the majority of those who become infected. This situation would seem to be related to the fact that the infected particle lodged in a nonvulnerable portion of the lung. This is not the complete story, however, for there was a small percentage of the cases in which the vulnerable portion of the lung became infected and the disease did not progress. Because data of the sort presented herein have not been given due consideration, the role of the lymph node in tuberculosis has been given a faulty interpretation.

This group of cases affords an opportunity to gain a clearer concept of tuberculous infection in general for the reason that the complicated morphologic picture encountered in persons with progressive disease is absent. The greatest

disappointment in the study of these cases was the failure to find an early non-necrotic lesion. Undoubtedly such lesions were present; probably they were too small to be recognized macroscopically. Of particular significance was the failure to find even one non-necrotic focus which was of sufficient size to make possible its detection in a roentgenogram of the chest. This point requires serious consideration relative to the early clinical case of tuberculosis. It is evident that early clinical tuberculosis does not resemble the early lobular pneumonia which is caused by most bacterial infections. The essential difference here is that early nontuberculous lobular pneumonia evidences no necrosis, whereas in early clinical tuberculosis both necrotic and non-necrotic lesions are present.

Pulmonary Tuberculosis Which Has Progressed to a Greater or Lesser Extent

This portion of the necropsy series is composed of 215 persons. All were more than twenty years of age. The morphologic picture was more complex in all of these persons than in the remainder of the necropsy series. They will be considered on the basis of the extent of the pulmonary disease and of the presence or absence of easily demonstrable open cavity formation. The data will be considered on the basis of macroscopic findings only.

Minimal Pulmonary Tuberculosis

The minimal pulmonary tuberculosis group consisted of 104 cases in which localized disease involved at least a cubic centimeter of lung parenchyma and in which no greater volume of lung tissue was involved than is designated in the *Diagnostic Standards* of the National Tuberculosis Association (1950 edition). Although no chest roentgenograms were available, the writer is of the opinion that all would have shown roentgenographic shadows which would be consistent with a diagnosis of minimal pulmonary tuberculosis on a clinical basis. A detailed study of this group of cases has been reported elsewhere (41), and only a few of the more significant findings will be discussed here.

All of the patients had multiple foci of disease, and the morphologic picture was far from uniform. Some patients showed only old calcified and fibrotic foci; some showed necrotic and non-necrotic lesions with little evidence of fibrosis; and some showed a much more complex picture. There was evidence in every instance that necrotic lesions were or had been present. A very few of the patients showed open cavity formation; they were included in the group because the cavities were less than 1 cm. in diameter. These cavities were so small that they probably would not have been apparent in chest roentgenograms.

Macroscopic evidence of lymph node involvement was found in 96 patients (92 per cent), and an attempt was made to divide this group into those of primary and those of reinfection disease. The patients considered to have had primary disease all had lymph node lesions limited to the direct line of drainage from the parenchymal disease and no disassociated calcific pulmonary or lymph node lesions. The patients considered to have had reinfection disease all had at least one calcified primary complex which was not in association with the lesion under study; and, if the lymph nodes draining the area of parenchymal disease were

tuberculous, the apparent age of the lymph node lesion approximated that of the parenchymal lesion under study. By the use of these criteria the entire group was separated into two subgroups: 41 cases of primary tuberculosis and 55 cases of reinfection disease.

Among the cases of minimal disease, the incidence of reinfection lesions in persons less than forty years of age was quite low (9 per cent) in contrast to the high incidence (73 per cent) in persons more than forty years of age. There was a considerable variety in the morphologic character of both the primary and reinfection disease which ranged from necrotic and non-necrotic foci to only fibrocalcific lesions. It seems reasonable to assume that lesions in which calcification was present, to a greater or lesser extent, were of older age than those in which there was no calcification. The distribution of the cases of primary and of reinfection disease on this morphologic basis, as well as according to age, is shown in table 2.

TABLE 2

DISTRIBUTION OF CASES OF MINIMAL TUBERCULOSIS ACCORDING TO AGE, TYPE OF INFECTION, AND PRESENCE OR ABSENCE OF CALCIFICATION AS PART OF THE MINIMAL DISEASE

Type of Infection	Number of Cases	Age in Years			
		Less than 40		More than 40	
		Without Calcification	Calcification Present	Without Calcification	Calcification Present
All cases	96*	17	6	49	24
Primary	41	16	5	10	10
Reinfection	55	1	1	39	14

* In the original paper, "Pathogenesis of Minimal Pulmonary Tuberculosis," only 96 of the 104 cases were classified as either primary or reinfection disease. The other 8 cases were indeterminate because a complete complex was not found. This table is consistent with the original text. However, the 8 unclassified cases are included in the data in table 1, which contains the essential gross data presented in the original paper.

The data in table 2 indicate that, whereas in the persons less than forty years of age primary lesions predominate, in persons more than forty years old, reinfection lesions predominate. Furthermore, this difference in the predominant type of lesion holds for both the necrotic and the calcific lesions. The obvious and, to the writer, the only explanation for this difference is that reinfection with tuberculosis is a not infrequent occurrence in middle and old age. If it were not, the differences noted would have to be explained alternatively on the basis that tuberculosis tends to progress to advanced disease more frequently in primary than in reinfection disease. A consequence of this explanation would be that among older persons the incidence of calcification would be higher in reinfection than in primary disease. The data in table 2 show quite the opposite; consequently, the alternative explanation is untenable. It is evident in the two age groups that there is no significant difference in the incidence of calcified lesions; neither is there any significant difference in the behavior of the disease.

The writer found it impossible, on microscopic study of parenchymal lesions, to differentiate between primary and reinfection disease.

The group was composed of 17 Negroes and 79 white persons. There were cases of primary and of reinfection disease in both groups. However, in the Negro group three-fourths of the cases were of the primary type and in the white group only one-third was primary disease. It is well known that Negroes with progressive disease have a high mortality rate, and it seems reasonable to assume that in many instances the disease was a primary infection. Those Negroes who had healed a primary infection could also have become reinfected, and the reinfection disease behaved quite like that in white persons.

The location of minimal pulmonary tuberculosis differed markedly from the scatter-pattern found in the calcified primary complexes. Eighty-four per cent of the persons with minimal disease had disease in the upper and dorsal portions of pulmonary lobes, whereas only 12 per cent of those with calcified primary foci had lesions in this region. The scatter was somewhat more widespread in the primary than in the reinfection minimal cases. One-fourth of the persons with primary disease had the parenchymal disease in the less vulnerable portions of the lung, whereas in the reinfection disease only one-tenth of the lesions were located in such areas.

Bilateral minimal tuberculosis was found in 18 per cent of the patients; in this respect there was no significant difference between the primary and reinfection groups. The paucity of cases of bilateral disease would make it appear that usually progressive pulmonary tuberculosis begins as a unilateral disease which for a variable time may remain quite localized in distribution. It was not possible to determine with accuracy whether the bilateral disease originated from bilateral aerogenous seeding or from endobronchial dissemination from one side to the other. However, the data from insignificant primary infections showed that aerogenous bilateral seeding was possible, and this feature should not be ignored in persons with progressive minimal disease.

In the group of 55 persons with reinfection disease, the primary focus was present in the intestines in 9 cases. A reinfection complex was present in 13 (24 per cent). It was shown above that, of the persons with healed complete primary complexes who also showed reinfection lesions, 10 (22 per cent) showed reinfection complexes. The term *reinfection complex* is used to signify that a necrotic lesion in the lung and in the draining lymph node is present in a person who also shows a complete complex in which both the parenchymal and lymph node components are calcified. This condition has been considered as almost nonexistent.

The finding of practically the same percentage of cases of this nature in both persons with insignificant reinfections and those with minimal pulmonary tuberculosis would hardly seem to represent either an error of interpretation or a chance finding. In most instances the necrotic lymph node component was minute and inconspicuous and would have been overlooked had not the routine procedure included a meticulous examination of all available lymph nodes. On several occasions the writer has seen necrotic lymph nodes in the line of

drainage of tuberculous ulcerations of the gut in persons who have died from pulmonary tuberculosis. It seems unreasonable to assume that necrotic lymph nodes can occur only in the line of drainage from a primary parenchymal focus. The reinfection complex was found in only 23 (2.5 per cent) of 889 cases of tuberculous disease of minimal or less than minimal extent; it is infrequent, but it does exist and should not be ignored.

In the 96 cases of minimal pulmonary disease, 115 different areas were involved. Of these, 101 were in the vulnerable portions of the lung and 14 were in less vulnerable areas. Calcification was present in 24 per cent of the lesions in the vulnerable areas and in 57 per cent of the lesions in the less vulnerable portions. This would suggest that there is a greater tendency for lesions to calcify in the less vulnerable portion. Two-thirds of the cases of minimal disease may be regarded, from the nature of the pathology, as having the potentiality for an increase of disease.

Evidence of tuberculous lesions in abdominal organs was found in 12 per cent of the cases of primary disease and in 4 per cent of the cases of reinfection disease. It is evident that a hematogenous seeding occurs more often in primary than in reinfection disease; however, in primary minimal disease a hematogenous dissemination is not a common affair.

Advanced Pulmonary Disease Without Cavity

The group of patients with advanced pulmonary disease without cavity consisted of 50 persons. In 3 there was evidence of generalized miliary tuberculosis; in 2, the lesions were of recent origin and probably soon would have become clinically evident, and one was an old healed affair. In the remaining 47 cases the disease appeared to be of long standing (Plate VI, figure 17), for in all there were present considerable parenchymal scarring, numerous calcified foci, and a variable number of necrotic lesions, most of which were only a few millimeters in diameter. In most instances the disease was bilateral.

Few, perhaps none, of these patients should be regarded as completely healed in a pathologic sense. On the other hand, it is probable that few of the lesions ever would have exhibited later a serious and sudden endobronchial extension. There were only a few patients with necrotic foci of sufficient size to make possible large extensions of new disease should they have undergone a considerable liquefaction and slough. However, in many of the cases it is conceivable that small endobronchial extensions from a partial sloughing of one or another smaller necrotic focus might have occurred from time to time. It is cases of this type which would fit neatly into the category of "the good chronic" of the phthisiologist.

Advanced Disease With Open Cavity Present

The group of patients with advanced disease with open cavity consisted of 61 persons. The extent of disease was in the clinical category of moderately and far advanced disease. A detailed report (39) of these cases has been given elsewhere and only a few pertinent remarks will be made here. All were cases of

"open" pulmonary tuberculosis, although several gave evidence that the disease was of long standing by the presence of considerable parenchymal scarring and numerous small calcific foci. In several the disease had the appearance of having developed recently, for there were no old foci and no parenchymal scarring. The morphologic features in these cases were equally as complex as those which would be found in persons who had died from tuberculosis, and no attempt will be made to go further into details of the pathology.

All of these persons were more than twenty years of age; 2 were less than thirty years old, 11 were between thirty and forty, and 48 (80 per cent) were more than forty years old. Of the 48 persons more than forty years of age, 47 were males, 45 of whom were white. The medical examiner's records show that in only 13 cases was death attributed to tuberculosis. In only 6 cases was it possible to determine that a diagnosis of tuberculosis had been made, and all of these persons had been under treatment for the disease at one time or another.

With few exceptions, the cavities were present in the superior and dorsal portions of pulmonary lobes. The pattern of cavity formation corresponded closely to the location of disease in minimal pulmonary tuberculosis, and in most instances the cavities could be regarded as first or primary cavities. Referring back to the time-sequence of events which was found in experimental tuberculosis, it seems probable that the cavities represented areas of tuberculous pneumonia which had undergone necrosis, liquefaction, and sloughing. This adds further evidence to the fact that, with individual exceptions, progressive pulmonary tuberculosis has its origin in the vulnerable portions of the lungs.

The data contained in this group of cases would seem to bear upon the epidemiology of the disease. In only 10 per cent of the group had the disease been recognized prior to death, and in only 20 per cent would the death records show death ascribed to tuberculosis. It is possible that this situation represents an exaggeration in the lack of recognition of open pulmonary tuberculosis. Nevertheless, these unrecognized cases are a potent source for the dissemination of the disease. Of particular significance is the age and sex distribution of the cases; 93 per cent of the group were white males more than forty years of age. This group equals 7 per cent of the white males more than forty years of age in the 1,000 necropsies. It may well be that the continuing new annual crop of tuberculous cases is related much more to the male more than forty years of age than is recognized at present.

The Apical Scar or Cap

This peculiar structure was not considered by the writer to be tuberculous in nature and, hence, was not used in the determination of the incidence of tuberculosis in the necropsy series. A detailed macroscopic study of the apical scar has been presented elsewhere (37) and only a few remarks would seem necessary here. These lesions were found to be bilateral in almost all of the cases in which they were present; they were found infrequently in persons less than thirty years of age and occurred most often in white males in the latter half of life. They occurred more often in whites than in Negroes. In 12 cases the lower

lobe was unusually long and occupied at least one-half of the dome of the chest. Six of these cases showed apical scars present over the apex of the lower lobe as well as over the apex of the upper lobe. These were the only instances in the entire series of 1,332 cases in which apical scars were found at the apex of the lower lobe; however, tuberculosis in this portion of the lobe was observed not infrequently.

Tuberculosis of the apices of upper lobes was observed in 95 cases. All of these tuberculous foci contained either necrotic or calcified foci or both types of lesion. In 43 there were obliterative pleural adhesions over the area, and no apical scars were found; in 20 there were neither pleural adhesions nor apical scars; and apical scars were involved in the tuberculous process in 33. As necrotic tuberculous lesions consistently occur early in tuberculous infections and as the healed remnants of necrotic foci are represented much more often by local calcific than fibrotic nodules, it was found that the presence or absence of a tuberculous lesion in relation to an apical scar was rather easy to determine. The association of tuberculosis with the apical scar was found in only 33 of 458 cases in which apical scars were found. The relationship of tuberculosis of the apices to apical scars is shown in table 3.

TABLE 3

RELATION OF TUBERCULOSIS OF APICES OF UPPER LOBES TO APICAL SCARS

Tuberculosis of Apices of Upper Lobes	Number of Cases	Apical Scars	
		Present	Absent
All cases	1,290	458	832
Tuberculosis absent	1,195	425	770
Tuberculosis present	95	33	62

The ratio of tuberculosis to the presence and to the absence of apical scars was identical. On this basis it appears evident that the apical scar bears no etiologic relationship to tuberculosis.

The study mentioned above was based upon macroscopic findings. A histologic study has since been made of apical scars from 50 persons in whom no evidence of tuberculosis was found and from 90 persons with evidence of tuberculosis. The latter group contained the persons in whom there was gross evidence of tuberculosis in the region of the apical scar. Lesions from persons in different age groups were included in the hope that the pathogenesis of the lesion might become apparent. Multiple areas from each scar were sectioned in each instance.

The intermixture or close association of tuberculosis with the apical scar was confirmed in the 33 cases so interpreted macroscopically. In the remaining 107 cases, no definite evidence of tuberculosis was found. In many of the lesions there were small collections of lymphocytes. None of the lesions had a structure which would be consistent with an organized focal pneumonic lesion. In some cases the lesion was predominantly a fibrotic thickening (Plate VI, figure 18) of the pleura, whereas in others the major component was an airless portion

(Plate VI, figure 19) of lung tissue. In some cases there were bronchi (Plate VI, figure 20) which seemed larger than one would expect to find so close to the pleura. Not infrequently lesions of this type showed small emphysematous bullae. In five of the specimens, bone formation was present; in four, the bone was a solid small piece (Plate VII, figure 21) within the parenchyma; and in one a piece of cancellous bone (Plate VII, figure 22) with bone marrow was present beneath the pleura. There was no evidence of calcific remnants with bone formation such as is commonly found in aged and healed calcific tuberculous foci.

Thus, the morphologic features of apical scars are more complex than would appear on macroscopic study, and the pathogenesis remains unexplained. It seems unlikely that such lesions are induced by an infectious process for the reason that usually there are no pleural adhesions over the scars, and in this series of necropsies there was little evidence of an acute pneumonic focus which was of such a limited extent. The microscopic study confirms the impression gained from the macroscopic study: etiologically, this lesion is not of a tuberculous origin (Plate VII, figure 23).

Variations in Interlobar Fissures

The data on this subject have been reported elsewhere (36) and will be commented upon only briefly. The data were collected for two reasons. Fissure lines are seen frequently in roentgenograms of the chest and in the past have been considered as evidence of interlobar adhesions. Also, there is a general belief that necrotizing pulmonary diseases, such as acute pulmonary abscesses and tuberculosis, extend across the pleura into another lobe.

The data on this subject showed that the major fissure on the left was incomplete in 18 per cent and on the right in 30 per cent; the minor fissure on the right was incomplete in 62 per cent. Frequently the minor fissure on the right had an unusual amount of connective tissue which extended inward beneath the pleura for a variable distance in the portion in which the fissure was not open. In such cases the pleura extended uninterruptedly over the area. It is the line of the right minor fissure that is most often observed in chest roentgenograms, and it seems probable that this line is visible because of the increased fibrous tissue in fissure lines which never had been open. This situation was found in infants as well as in adults and in persons in whom there were no pleural adhesions or significant pulmonary pathology.

The fissures were so incomplete in 145 lungs that the organ could be considered as a single lobe. In such lungs, practically the only barriers to prevent the extension of an infectious process from one lobe of the lung to another would be alveolar walls. It is in lungs of this structure that the writer has seen tuberculous cavities, acute lung abscesses, and lobar pneumonias that have extended across the area which normally would be separated by pleura. Not a single instance has been encountered in which large areas of two adjacent pleural surfaces have been destroyed in the formation of tuberculous cavities. Several large tuberculous cavities have been observed, however, which were in different lobes and

were separated only by thickened pleura plus fissures obliterated by pleural adhesions. The infrequency of pleural fistulas in pulmonary tuberculosis attests to the fact that the pleura is a very effective means of preventing infection of the pleural space. The pleura, when present, is equally effective in preventing a direct extension of disease from one lobe to another.

A considerable variation in size of lobes was noted; however, extreme variations were rare. Two cases were observed in which an extreme variation would lead to an erroneous interpretation of the location of tuberculous cavities. In these cases the lower lobe was unusually long and its apical portion occupied approximately one-half of the dome of the chest. A tuberculous cavity was present in each patient in that location which usually would be considered to be in an upper lobe. The variation in size of lobes also influences the location of fissures.

Extra fissures occurred, but they were rare and were usually incomplete. Azygos "lobes" were noted seven times; these are not lobes but are deep grooves in the upper lobe which are caused by a shelf of connective tissue which supports the azygos vein in its free border. The peculiar roentgenographic shadow seen in such cases would seem to be caused by the band of dense fibrous tissue in the shelf; not the pleural coverings.

Additional Observations Unrelated to Pulmonary Tuberculosis

A few features of interest but with no relation to pulmonary tuberculosis will be briefly mentioned. Pleural adhesions were commonly found in cases of advanced tuberculosis. They were also present, to a greater or lesser extent, in one-sixth of the cases in which minimal or less tuberculosis or no evidence of tuberculosis was present. In most instances the patient with minimal tuberculosis showed no pleural adhesions over the involved area.

Phleboliths were found in 20 cases. These structures were fairly easily recognized by their smoothness and round or oval shape. They were easily expressed by cutting through the vessel wall.

In 9 cases, abnormally large pieces of cartilage were found well out in the lung parenchyma. Most of them were in lower lobes, and in one case the condition occurred bilaterally. The largest piece of cartilage measured 1.5 cm. in diameter. Whether structures of this nature represent neoplasia or local maldevelopment of the lung is a moot question.

Malignant tumors, largely carcinomas, were found in 48 cases; 9 were primary carcinomas of the bronchi and the remainder were primary in various other organs. In a very few of these there were metastases, sometimes extensive, in the lungs. Malignancies would naturally be expected to be present, as two-thirds of the patients were adults more than forty years of age.

Easily identified bronchiectasis was found in a few cases, but a careful study of this condition was not made. Two cases of cystic bronchiectasis of the upper lobes were noted. One of these patients had been treated for advanced pulmonary tuberculosis twenty years previously and had been carried continuously as a tuberculous case by the New York City Board of Health although no tu-

bercle bacilli had ever been isolated. The second case was that of a young Negro woman who was listed as having died from pulmonary tuberculosis. Macroscopically, the lesion was mistaken for a multilocular tuberculous cavity; however, microscopic study corrected this misconception.

Acute lobular or lobar pneumonia was noted in 52 cases. Purulent bronchitis was seen not infrequently, but no careful record of this condition was kept.

As spontaneous pneumothorax is sometimes considered, clinically, to be either associated with or caused by tuberculosis, data on this subject were collected in the necropsy series. A total of 66 cases of emphysematous bullae were found; 31 were not associated with either tuberculosis or apical scars; 30 were associated with apical scars (Plate VII, figure 24) in which there was no evidence of tuberculosis; and 5 were associated with evidence of tuberculosis. Usually the bullae were in the apical region and commonly they were bilateral. Sometimes the patients with bullae in the absence of tuberculosis and apical scars had smaller bullae, often in considerable numbers, near the thin free edges of pulmonary lobes.

Tuberculosis is apparently a rare etiologic factor in bullae formation. Although in half of the cases the bullae were in direct association with apical scars, it would appear that this lesion is not often an etiologic factor. In 458 persons in whom apical scars were found, only 34 showed bullae present. The youngest person in whom bullae were found was sixteen years of age and the oldest was eighty-six years old. A thorough microscopic study of the tissue in which bullae were present was not made, and further comments on this interesting pathologic process are not warranted.

Progressive Primary and Reinfection Tuberculosis as the Cause of Death

During the twenty-year period prior to the time this work was done, tuberculin surveys of children and of young adults showed that a considerable decrease had occurred in the incidence of reactors. In spite of this change, tuberculosis continued to be listed as the chief cause of death among infectious diseases in the age group between twenty and thirty-five years. When the writer first began to study the morphologic aspects of tuberculosis at Bellevue Hospital in 1944, he was struck by the similarity of the pulmonary disease in some persons who died from tuberculosis in the seventh decade of life with that found in persons in the third decade. These two phenomena suggested the desirability of an attempt to determine the incidence of progressive primary and of progressive reinfection pulmonary tuberculosis as a cause of death in adults.

One hundred consecutive necropsies on patients who had succumbed to tuberculosis were examined. These patients were in large part from the Chest Service of Bellevue Hospital. The technique was the same as that used in the study of the larger series from the medical examiner's cases. A detailed report of this study has been made elsewhere (38), and only a few pertinent remarks will be presented here.

It soon became evident that little reliance could be placed upon the findings of small parenchymal foci, calcified or necrotic, as evidence of a primary pulmonary lesion. Cavitation usually was so extensive that a minute primary

calcific focus might easily have been sloughed. In some of the patients there were numerous small calcified foci which probably were related to the chronicity of the disease rather than to primary lesion or lesions. Because of this situation it was necessary to rely entirely upon the evidence of tuberculosis found in lymph nodes as a basis for determining whether the disease was one of primary or of reinfection origin.

The occurrence of only necrotic foci in lymph nodes was accepted as evidence that the disease was of primary origin. Not infrequently the necrotic lymph node focus was so small that it would have been overlooked without a thorough investigation. On the other hand, large, completely necrotic lymph nodes were easily found. The latter condition was more often observed in Negroes; however, this does not suggest to the writer that a racial factor need be used to explain this situation.

The occurrence of only calcified lesions in lymph nodes or of calcified and necrotic foci in unrelated lymph nodes was accepted as evidence of reinfection tuberculosis. Here again, not infrequently the calcific and the necrotic foci were so small that they would have been easily missed without a meticulous search. Larger calcific and necrotic lymph node lesions were easily demonstrated. This situation was found predominantly in white persons.

Using these criteria, the group of 100 cases was divided into 34 of progressive primary disease and 45 of progressive reinfection disease; in 21 cases no lymph node lesions were found and these remained as unclassified. In the age group between sixteen and thirty years, there were 16 cases; 75 per cent were primary, 13 per cent were reinfection, and 12 per cent were unclassified disease. Thirty-five of the patients were more than fifty years of age; 6 per cent of the infections were primary, 71 per cent were reinfection, and 23 per cent were unclassified disease. This difference in the occurrence of primary and of reinfection tuberculosis in these two age groups indicates to the writer that progressive primary pulmonary tuberculosis is largely the cause of death in adults less than thirty years of age and that progressive reinfection disease accounts, in large measure, for tuberculous deaths in persons more than fifty years of age. In the 100 necropsies, 49 of the patients were between thirty and fifty years of age: 20 of the infections were primary, 18 were reinfection, and 11 were unclassified cases.

In 17 cases a reinfection complex was found, that is, a necrotic lesion which was present in a lymph node that was not related to the one with a calcific lesion. In several instances both the necrotic and the calcific foci would have been overlooked had not a prolonged search for evidence of tuberculosis in fresh lymph nodes been made.

Unless some reliance can be placed upon the occurrence of only necrotic lymph node lesions as evidence of a primary infection and of only calcified lesions as evidence of reinfection, then it becomes impossible to differentiate between primary and reinfection tuberculosis. By the same token the presence of both necrotic and calcific foci in unrelated lymph nodes would not constitute evidence of either primary infection or reinfection. This is well shown in one case in this study in which a bone-hard calcified lymph node was present in the mesentery and a good-sized necrotic lymph node was present in the hilar region of the lung.

An estimation of the approximate age of lymph node lesions is one of fundamental importance in a pathologic interpretation. It applies with equal force to the person in whom a solitary necrotic or calcific primary complex is the only evidence of demonstrable tuberculous disease as well as to the presence of a calcific, or necrotic, lymph node focus in a person who succumbs to the disease. On purely pathologic grounds, the writer is of the opinion that the distinctions made in this group of cases are valid; on the other hand, it is infrequent that a distinction between primary progressive and reinfection progressive pulmonary tuberculosis can be made in adults on the basis of roentgenographic evidence of enlarged hilar lymph nodes.

Significant Data Obtained from General Necropsy Files

The last study undertaken during the writer's sojourn in New York City was a search of necropsy files in general hospitals for evidence of significant pulmonary tuberculosis. This study has been reported elsewhere (35, 40) and only a few remarks will be made here. The finding of undiagnosed cases of tuberculosis with open cavities in the medical examiner's series made the writer wonder how much significant pulmonary tuberculosis might be hidden in general necropsy records, that is, those cases in which the principal cause or causes of death did not include tuberculosis. In this study, more than 17,000 necropsy records were examined in three large municipal and four large voluntary hospitals. All necropsy records were included irrespective of the causes of death.

These necropsy records are entirely unsuitable for a study of the incidence of tuberculosis. In this study, patients were regarded as having significant tuberculosis only if at least a necrotic lesion more than 0.5 cm. in diameter was recorded. Necrotic lesions of this size or larger have at least some potential significance and should not be regarded as healed disease. It was soon found that the necropsy record of the lung findings had to be read in all cases in which tuberculosis was not listed as the cause or a contributing cause of death. "Fibrocaseous" tuberculosis might be listed, and the description of the lung would show that cavity formation also was present. An obsolete tuberculosis might be either an apical scar or a number of "caseous" foci, and on occasion significant tuberculous foci would be described in the lung and no listing of tuberculosis given in the pathologic diagnoses. These lapses in the listing of anatomic diagnoses are not to be wondered at in hospital necropsy files for, in general, the pathologic features which are of chief interest are those obviously related to the cause of death. Extensive review of the necropsy records was necessary in order to obtain the facts which were sought.

In comparing all necropsy records of 1916–1920 with those of 1940–1945, a considerable shift in the age distribution of the necropsy material had occurred. In 1916–1920, 35 per cent of the patients were less than ten years of age and 32 per cent were more than fifty years of age. In 1940–1945, 8 per cent of the patients were less than ten years of age and 60 per cent were more than fifty years of age. A shift of this nature was found in all hospitals and should be borne in mind in any consideration of the problem of tuberculosis.

Significant tuberculosis in the necropsies of 1916–1920 was found in 12 per

cent of patients less than ten years of age and in 25 per cent of patients more than fifty years; in 1940–1945 the percentages for these two age groups were 6 per cent and 20 per cent, respectively. In the latter period, necropsies performed on tuberculous patients from chest services were excluded because all hospitals did not have such services. Thus, there was a marked decrease in the incidence of significant tuberculous lesions in the age group less than ten years in contrast to a modest decrease in the age group more than fifty years when the records of the two periods were compared. There was a shift in the age distribution of necropsy cases with significant tuberculosis, which perhaps reflected the shift in age distribution found for necropsies as a whole.

In going over the records it was noted that at times a considerable amount of pulmonary tuberculosis was found at necropsy without a clinical diagnosis of tuberculosis. In 117 cases of this nature, 81 per cent of the patients were more than fifty years of age. In the entire necropsy series at Bellevue Hospital between 1935–1944, 1 per cent of the group showed open tuberculous cavities in persons who had died from causes other than tuberculosis and in whom a clinical diagnosis of tuberculosis had not been made. Of this group, 88 per cent were more than fifty years of age; 92 per cent were whites and 90 per cent were white males.

These data would indicate that in general hospitals there is an appreciable number of persons in the older age groups who harbor unhealed tuberculosis and that not infrequently a clinical consideration is not given to the possibility of open cavitary tuberculosis. A somewhat similar situation was found in the necropsies performed by the medical examiners. The results of the study of the necropsy records have a direct bearing on the public health problem of tuberculosis control. The data presented are of such a nature that they would not be included in the usual reporting of vital statistics.

GENERAL COMMENT

It will be left to the judgment of the reader to decide whether it was worth while to spend four rather strenuous years in the collection of the data which has been presented. As a pathologist, the writer's concept of tuberculous infection in man now differs radically, in some respects, from the concepts which he was taught. Admittedly, this is due in a considerable degree to the time-sequence of events which was found in experimentally produced tuberculosis. The group of cases studied does not contain as many persons less than twenty years of age as would be desirable. This situation applies to all necropsy series, however, because of the considerable decrease during the past thirty years in deaths from all causes in this age group. A sufficient sample of all age groups more than twenty years was examined so that a glimpse of the incidence and nature of tuberculous disease in a large metropolitan area was obtained. It is not held that the situation found can have universal application. Tuberculous infection is unevenly distributed in any large population. It is a herd disease and, as a result, large congested areas of population in all probability would have the highest incidence both of infection and of deaths from the infection.

The most significant fact of all is that, although the tubercle bacillus fre-

quently succeeds in creating a new home for itself, it fails almost as frequently to maintain its residency. This feature would seem to be related to the fact that it is a common air-borne infection and also to the fact that the bacilli frequently fail to lodge in the "vulnerable" portion of the lungs.

Another fact of great significance is that the disease begins as a minute focus in the alveolar portion of the lung; it commonly begins as a single focus, but it may also begin as multiple widely separated foci. The number of initial foci may, perhaps, be related to the amount of pollution of the air, at the time of inhalation, with minute particles which contain viable, pathogenic tubercle bacilli. No evidence was found which would support the thesis that a massive infection arises directly from an air-borne source.

The earliest macroscopically detectable lesion is a minute necrotic focus of lobular tuberculous pneumonia, and it is the behavior of this lesion which determines the course of the disease. If liquefaction and sloughing do not occur, the end result is usually a calcific healed focus. If liquefaction and sloughing do occur, the disease may be disseminated within the lung locally first; but later, with liquefaction and sloughing of larger lesions, massive, widespread disease may develop. The extent of pulmonary parenchyma involved and the size of the areas of dissemination are the only distinguishing features between minimal and far advanced disease. Liquefaction and sloughing of a minute necrotic focus are a prerequisite for the development of minimal pulmonary tuberculosis. Liquefaction and sloughing of an initial minute necrotic lesion occur commonly if the lesion is located in the vulnerable portions of the lung; they occur rarely if the lesion is situated in less vulnerable areas. This applies to adults; however, from the writer's limited experience, it does not appear to apply to infants and young children.

Primary infection usually extends far enough to infect lymph nodes in the direct line of drainage. Usually a further dissemination does not occur; tuberculosis does not become a generalized disease with any great frequency. Again this applies to adults much more than to young children. No evidence was found to support the thesis that latent post-primary lesions occur frequently and are the source from which progressive pulmonary tuberculosis develops many years later. The hematogenous dissemination which does occur in a small percentage of primary infections can account for the occasional cases of bone, joint, or renal tuberculosis which show no roentgenographic evidence of a pulmonary tuberculous infection.

Lymph node involvement is common in primary tuberculosis. Except in babies and in certain races, i.e., Negroes, the extent of involvement usually is of a minor nature and commonly heals completely by calcification and fibrosis. Lympho-hematogenous dissemination of the disease is much less frequent than hematogenous; it does occur and is manifested by a generalized miliary tuberculosis. No evidence was found which would substantiate the dogma that focal, apical, lympho-hematogenous seedings are the source from which progressive pulmonary tuberculosis develops.

Primary progressive and reinfection progressive pulmonary tuberculosis are real entities. It is the writer's opinion that confusion on this subject can be laid to a lack of thoroughness in the examination of lymph nodes. Failure to recognize reinfection complexes which sometimes are encountered in reinfection disease can also be laid to an insufficient search for evidence of lymph node involvement. Progressive primary pulmonary tuberculosis accounts for the large majority of clinical patients less than forty years of age; it is found less frequently in older persons. Progressive reinfection pulmonary tuberculosis accounts for the majority of clinical tuberculosis in persons more than forty years of age; it does occur, however, in an occasional person between the ages of twenty and thirty. This situation makes little difference in the clinical management of tuberculous patients except that, in progressive primary tuberculosis, hematogenous dissemination occurs with greater frequency than in progressive reinfection disease. Epidemiologically, the prevalence of the two entities in different age groups greatly complicates the problem. No age group can be regarded as safe from a progressive tuberculous infection, even if the patients have completely healed previous infections.

The data which have been presented were obtained largely from necropsies on persons who had not died from tuberculosis. This is essential to obtain a well-balanced concept of the disease. Too much reliance has been placed upon studies based only on necropsies on persons dead from tuberculosis; generalizations based upon such studies are to a considerable extent responsible for confusion in the understanding of the disease. This concerns in particular the concepts accepted by those who manage the clinically ill tuberculous patient. It would appear that only a minor percentage of persons who become infected with tubercle bacilli ever develop a progressive disease. This needs careful consideration if a warped view of the problem is to be avoided. It is a common clinical teaching that tuberculosis usually is a generalized disease. The data presented in this study of necropsies do not confirm this concept. It would be more accurate to state that persons who become infected with the tubercle bacilli and who do not develop progressive pulmonary tuberculosis seldom have hematogenous disseminations; persons who develop progressive pulmonary tuberculosis and do not die from the infection not infrequently do not have a generalized dissemination of the disease, and persons who succumb to tuberculous infection commonly show a generalized dissemination of the disease.

A consideration of the histopathologic features in pulmonary tuberculosis as found in necropsy studies will be integrated with the data obtained from the study of resected pulmonary tuberculous tissue.

PLATES V–VII follow

PLATE V

FIG. 13. (× 15) White male, age sixty-one. Single primary complex. Parenchymal component illustrated. Lesion was near base of right lower lobe and was 3 mm. in diameter. Note bone and bone marrow formation about calcified central portion. This ancient primary complex was the only evidence of tuberculosis.

FIG. 14. (× 5) White male, age thirty-seven. Tuberculosis of minimal extent in right upper lobe. Parenchymal disease consisted of several necrotic lesions which were localized in the superior and posterior portions of the posterior segment. Illustration shows the only lymph node lesion found. A necrotic lesion occupied the major portion of a lymph node which measured 5 mm. in greatest dimension. No tuberculous disease other than the primary minimal tuberculosis was found.

FIG. 15. (× 15) White male, age fifty-one. An ancient primary parenchymal focus was present in the lower and anterior portion of the left upper lobe. A 2 cm. necrotic lesion and several smaller necrotic foci were present in the superior segment of the left lower lobe. Two lymph nodes with small necrotic lesions similar to those in figure 14 were found adjacent to the bronchus of the left lower lobe. This was the only evidence of tuberculosis found. Case is regarded as a reinfection minimal tuberculosis with a reinfection complex. Illustration shows lymph node of ancient primary complex of the upper lobe. Note bone and bone marrow formation peripheral to the large calcified area in the upper portion to the right. This node was the only node involved in the upper lobe. It measured approximately 5 mm. across and was easily palpated.

FIG. 16. (× 10) White male, age eighty-one. An ancient primary complex was present in the lower portion of the left upper lobe. Also there were nine 2 to 4 mm. necrotic foci scattered in four of the five pulmonary lobes. No lymph node lesions other than the old calcified one of the primary complex were found. There were small bilateral apical "caps." The illustration shows one of the small necrotic lesions and a section through the "cap" at the apex of the left upper lobe. The necrotic lesion is the only one which was located in the upper portion of a lobe. No pleural adhesions were present over the "cap." No evidence of tuberculosis was found aside from the pulmonary foci. The necrotic lesions are regarded by the writer as reinfection disease.

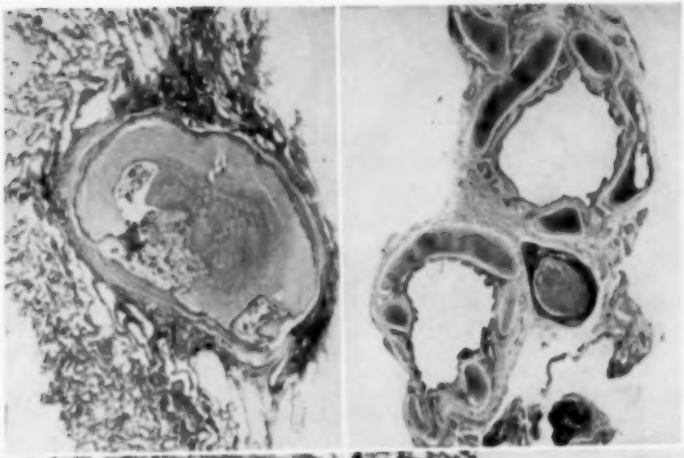


Fig. 13

Fig. 14

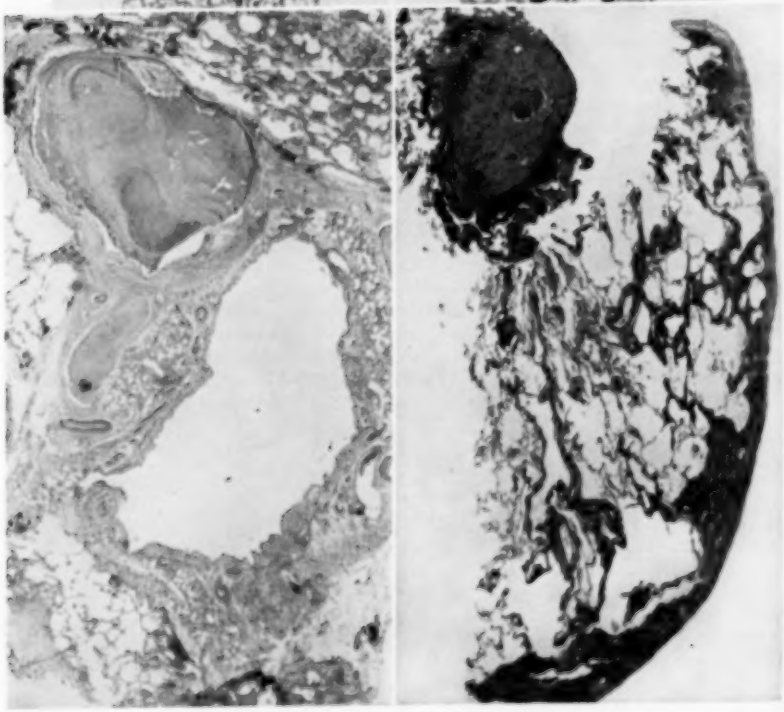


Fig. 15

Fig. 16

PLATE V

PLATE VI

FIG. 17. (× 2) White male, age sixty-two. There was considerable involvement of both upper lobes, and much the same picture was found on both sides. The tissue illustrated had to be decalcified prior to sectioning. It shows rather extensive parenchymal scarring which in some areas contained densely calcified old necrotic foci. To the left beneath the pleura are necrotic pneumonic lesions which are undergoing liquefaction. In the lower portion there are tubercles and smaller necrotic lesions. Some obstructive emphysema may be noted in the parenchyma which is not directly involved in the tuberculous disease. No macroscopic evidence of lymph node involvement was found. It is evident that the person had had tuberculosis for a long time. Death was due to violence. No clinical diagnosis of tuberculosis had ever been made.

FIG. 18. (× 15) This is an apical cap from the patient observed in figure 15. Apical caps were present on both sides and showed a similar structure. Note that in this case the lesion consists of a dense fibrotic thickening of the pleura beyond a narrow zone of dense lung tissue. No adhesions were present over these lesions.

FIG. 19. (× 15) White male, age sixty-one. Only evidence of tuberculosis was a single ancient primary complex in the left lower lobe. There were large bilateral apical caps over which there were no adhesions. Illustration shows about one-fourth of the diameter of one of the caps. In this instance the pleura is not thickened.

FIG. 20. (× 10) White male, age sixty-four. The only evidence of tuberculosis in this patient was an old small necrotic, but not calcified, primary complex in the lower portion of the right lower lobe. There were large bilateral apical "caps." The illustration shows an unusually large bronchus and vessel for the region in which they are present. The bronchus was empty; it showed no evidence of inflammation and no evidence of an obstruction was found. To the upper left of the bronchus there are three bronchi which are filled with clear mucus. The epithelial lining of these bronchi is considerably flattened. Apparently there are small bronchial cysts. There is no evidence of lung structure in large areas of the fibrous tissue beyond the large bronchus. No pleural adhesions were present over the region of the "caps."

FIG. 17

FIG. 18

FIG. 19

FIG. 20

PLATE VI

PLATE VII

FIG. 21. (× 15) White male, age sixty. No evidence of tuberculosis was found. Small bilateral apical caps were present with no adhesions over the lesions. Illustration shows a small piece of solid bone 2.5 cm. from the top of the illustration. The writer has never seen this type of bony metaplasia in an ancient tuberculous focus. Note the several small bullae within the lesion.

FIG. 22. (× 10) Negro male, age fifty-eight. No evidence of tuberculosis was found. Bilateral apical "caps" were present and there were no pleural adhesions. Illustration shows a small portion of one of the "caps." Note the cancellous bone with bone marrow formation in the upper central portion. This appears to be within the lung as there is a slightly thickened pleura covering the area. The writer has not found either bony metaplasia of this shape in an ancient tuberculous focus or this change without there also being present calcific remnants which were not present in this instance.

Note also the two cystic spaces which were in association with, rather than an integral part of, the "cap" structure. These were clean-appearing cysts without epithelial linings and also without evidence of fenestrations which usually are noted in bullae found in association with parenchymal scarring.

FIG. 23. (× 10) Negro male, age forty-three. The lesion illustrated was at the apex and was assumed to be an apical "cap." The whorled appearance within the parenchymal scar, the considerable deposits of anthracotic pigment, and the presence of small bits of calcification indicated that it was a healed tuberculous process. No evidence of active tuberculosis was found. Note the presence of lung parenchyma between the pleura and the scar in one portion. This situation is found not infrequently in tuberculosis, even where, macroscopically, tuberculous cavities seem to extend directly to the pleura.

FIG. 24. (× 2) White male, age fifty-five. No evidence of tuberculosis was found in this case. Sizable fenestrated bullae were present in each apical region. Macroscopically there did not appear to be any apical "caps." The illustration suggests that small apical caps were present and that, with the formation of the large bullae, the structure of the "cap" was so altered that it was not recognizable macroscopically. In other instances the involvement of the "cap" can be recognized grossly. Rarely are there any pleural adhesions over the area where these bullae are present. This is quite in contrast to the bullae found in tuberculous lungs with considerable parenchymal scarring for, here, pleural adhesions usually are present.

FIG. 21

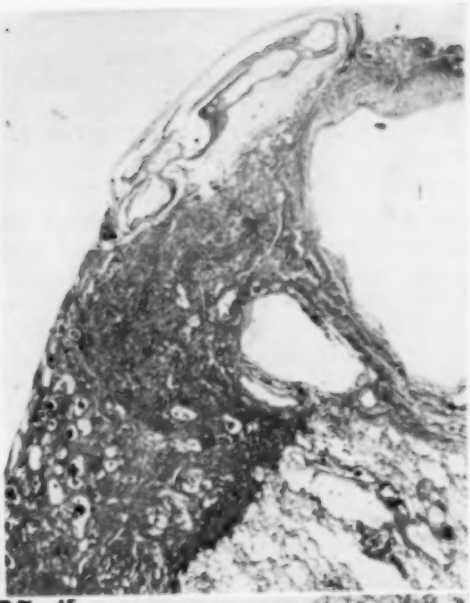


FIG. 22

FIG. 23

FIG. 24

PLATE VII

CHAPTER IV

PRELIMINARY DISCUSSION OF RESECTED SPECIMENS

In the preceding chapters the groundwork has been laid for a discussion of the dynamics of tuberculous lesions as found in surgically resected human tuberculous lung tissue. In the experimental studies it was found to be possible, through the use of artifices, to reproduce the essential morphologic features observed in human pulmonary tuberculosis. It was found that necrosis of lobular tuberculous pneumonia occurred fairly early in the disease and that a prerequisite to sloughing and cavity formation was liquefaction of the necrotic lesion. In the process of liquefaction there was a second invasion of neutrophils, and the liquefied debris was sloughed through connecting bronchi, thus enabling a greater dissemination of the disease within the lung. Under suitable experimental conditions, the higher portion of the lung parenchyma was found to be more "vulnerable" than other areas to progressive disease.

From the necropsy studies a broad view of human tuberculous pulmonary infection was obtained. Here it was found that in approximately four-fifths of the infected persons the infection failed to progress. In those persons with progressive tuberculosis, the extent of the disease ranged from a small well-localized area to an extensive involvement of both lungs which was fatal. It was unusual to find that the disease had progressed to a state of "minimal" pulmonary tuberculosis outside of the superior and posterior portions of pulmonary lobes. Although minimal disease involved only a small portion of lung parenchyma, the morphologic features sometimes were as complex as in advanced disease. From the evidence obtained experimentally, one may assume that these areas were the most "vulnerable" portions of the human lung. Even in the "vulnerable" portion of the lung there was evidence that in many persons the disease had not progressed further than a "minimal" localized pulmonary disease which eventually healed completely.

The morphologic features of the disease in the persons who showed progressive disease were so complex that, without a knowledge of the time-sequence of events observed in the experimental studies, it would not be possible to gain a clear understanding of the pathologic process. This knowledge was especially valuable in considering the problem of progressive primary and of progressive reinfection tuberculosis, both of which are regarded by the writer as exogenous air-borne infections. The evidence indicates that progressive primary tuberculosis accounts for the large majority of tuberculous persons who are less than forty years of age and that progressive reinfection disease predominates in persons more than forty years of age.

A discussion of the histopathologic features of tuberculous lesions found at necropsy has been postponed in order that the resected tuberculous pulmonary tissue could be included. Most of the surgical specimens were removed from pa-

tients who, with individual exceptions, had had chemotherapy for a few to many months. Moreover, chemotherapy is known to influence the clinical course of pulmonary tuberculosis. Hence, it seems pertinent to present the major histopathologic features of progressive pulmonary tuberculosis in patients without such treatment. With rare exceptions, necropsy material is the only source for a study of the disease which has been unaltered by clinical treatment. Accordingly some of the illustrative cases in the following chapters are from necropsies performed prior to the era of chemotherapy.

BASIC DATA ON RESECTED SPECIMENS

The surgical specimens were obtained during the period from 1949 to 1953 at Sunmount Veterans Administration Hospital, Saranac Lake General Hospital, Ray Brook Sanatorium, and Hermann M. Biggs Memorial Hospital. These specimens have been meticulously studied macroscopically, microscopically and, in a considerable number, bacteriologically. The specimens were from 313 patients, of whom 271 had unilateral and 42 had bilateral resections. The age and sex distributions of the cases are shown in table 1.

TABLE 1

SEX AND AGE DISTRIBUTION OF 313 PATIENTS FROM WHOM PULMONARY TISSUE HAD BEEN RESECTED

Specimens Obtained from Sunmount Veterans Administration Hospital, Saranac General Hospital, Ray Brook Sanatorium, and Hermann M. Biggs Memorial Hospital

Institution	Sex	Total Cases	Ages in Years					
			0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50+
All hospitals	All cases	313	1	34	107	111	44	16
	Male	184	1	12	58	66	33	14
	Female	129	—	22	49	45	11	2

It is of interest that 80 per cent of the patients operated upon were less than forty years of age. This represents selection by the clinicians and surgeons of the younger patients as candidates for surgery. Such considerations as pulmonary and cardiac status and the extent of the roentgenographically evident residual disease after prolonged chemotherapy bore heavily upon the selection of candidates. With few exceptions, surgery was not advised until negative bacteriologic findings were obtained. There were 293 white persons and 20 were nonwhites. The amount of tissue which was removed is shown in table 2.

TABLE 2

PULMONARY TISSUE RESECTED IN 313 PATIENTS

Amount of Tissue Removed	Number of Specimens	Right Lung	Left Lung
Wedges of segments	276	144	132
Segments of lobes	148	91	57
Lobes of lung	111	83	28
Complete lung	19	13	6

Of the 276 wedges of segments, 199 (72 per cent) were removed from the "vulnerable" portions of lobes and the remaining 77 were about equally distributed between the anterior and lingular segments, middle lobe, and basal segments of the lung.

There were 115 apical, posterior, or apico-posterior segments of upper lobes, 32 superior segments of lower lobes, and one superior division of lingula of the left lung. In these cases, wedges or local excisions also were removed not infrequently from other portions of the lung. It is of no small interest, however, that in these patients, most of whom had had advanced disease, the major amount of disease which persisted, even under prolonged chemotherapy, was limited to the "vulnerable" portion of pulmonary lobes.

Of the 111 pulmonary lobes, 73 were upper, 19 were middle, and 19 were lower lobes. A clinical diagnosis of either bronchiectasis or chronic lung abscess was made in 18 patients, and a diagnosis of bronchiectasis and tuberculosis in 4 patients. Of these 22 lobes, 5 were upper, 6 were middle, and 11 were lower lobes.

Two of the pneumonectomies were emergency procedures due to the tearing of blood vessels. In 2 cases, the major pathology was bronchiectasis which had not been recognized prior to operation. The remaining 15 lungs showed extensive tuberculous involvement.

The nature of the pathology found in the resected specimens and the age distribution of the patients may be seen in table 3.

TABLE 3

NATURE OF PATHOLOGY FOUND IN 313 CASES

Age Distribution of Cases Shown

Nature of Disease	Number of Cases	Age in Years					
		0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50+
All specimens	313	3	32	107	111	44	16
Tuberculosis only	269	1	27	98	97	34	12
Tuberculosis and bronchiectasis	26	—	4	8	7	7	—
Bronchiectasis only	18	2	1	1	7	3	4

Of particular interest was the occurrence in 8 per cent of the tuberculous patients of progressive tuberculosis in association with bronchiectasis. In most instances the bronchiectasis had not been recognized prior to operation. This group of patients together with 18 persons who were operated upon for bronchiectasis or chronic pulmonary abscess without clinical evidence of tuberculosis will form the basis for a discussion of bronchiectasis in a future chapter.

The clinician and surgeon probably will be interested most in the effects produced by chemotherapy on the morphology and bacteriology of surgically resected tuberculous lung tissue. On the other hand, the pathologist and the bacteriologist should not limit their interest solely to the possible effect of chemotherapy. In the group of 295 tuberculous patients under study, tissues have been removed three months to twenty years after a first clinical diagnosis of

tuberculosis was made. In general the clinician is more apt to use chemotherapy in patients with recently discovered, clinically acute disease than in patients who have been known to have had disease for a number of years. This is understandable; however, the pathologist is well aware of the fact that pulmonary tuberculosis commonly smolders for an indeterminate period prior to clinical recognition. This situation requires that both the pathologist and the bacteriologist constantly bear in mind the time-sequence of events in pulmonary tuberculosis.

Necrotic lesions precede liquefaction and liquefaction precedes the sloughing from which endobronchial dissemination within the lung becomes possible. Many necrotic lesions may long antedate both the time of discovery of the tuberculosis and the institution of chemotherapy. The morphologic features and the bacteriologic findings in necrotic lesions may well have been established prior to the institution of a chemotherapeutic regimen.

Although the disease process usually is considerably altered in a favorable direction by the proper use of chemotherapy, the tissues resected during such treatment afford the pathologist an opportunity to study the dynamics of the disease at stages which hitherto have been unavailable. This provides an incentive to examine carefully the potentialities of the residual disease and in this way define clearly any problems which chemotherapy or other therapeutic measures have not solved.

THE NATURAL COMPONENTS OF PROGRESSIVE PULMONARY TUBERCULOSIS

The writer is of the opinion that pulmonary tuberculosis can best be understood on a basis of inflammation and of repair of injury to the lung structure. If the disease becomes progressive, it would seem reasonable to apply the time-sequence of events which has been determined in the experimental host. In the necropsy study the writer was unable to find an *initial* lesion in a prenecrotic state. This would suggest that such foci either were absent or were too small to be detected macroscopically. As a result, material is lacking by which to illustrate this phase of the disease in man. In the experimental host, however, this microscopic lesion was found to be an area of lobular pneumonia in which the predominant cellular element was the neutrophil.

> The earliest progressive pulmonary tuberculosis which the writer has observed occurred in a sixteen-month-old white female infant who died from generalized miliary tuberculosis and meningitis a few days after admission to the hospital. At necropsy the lungs were uniformly seeded with minute foci which were more easily felt than seen. There was a single 5 mm. firm slightly yellowish-gray lesion in the lower and anterior portions of the right upper lobe. A single lymph node, firm and easily movable, lay adjacent to the right upper lobe bronchus in line of drainage of the large parenchymal focus. On section it was of a rubbery consistency and of a yellowish-gray color; it measured 1.0 by 0.5 cm. on cross-section. Numerous other hilar lymph nodes were more prominent than normal, but they appeared to be merely hyperplastic.

Microscopic study showed that the numerous minute lesions palpated in the lung were all small focal areas of open lobular pneumonia (Plate VIII, figure 26). These minute foci had the structure of miliary abscesses. The neutrophil was the predominant cellular element, although monocytes were also present. Even though many lesions were in the early phase of necrosis with beginning disintegration of the neutrophils and monocytes, no lesion was wholly necrotic. From the histologic picture alone it was not possible to determine that these lesions had arisen from a hematogenous seeding. There was no evidence of a walling off of the lesions by fibrous tissue. Perhaps lesions of slightly different age were present, for in many there was no evidence of necrosis. In the lung parenchyma not directly involved in these lesions, alveoli which contained numerous monocytes and some serous exudate were present. No "epithelioid" tubercles or giant cells were found.

The large lesion (Plate VIII, figure 25) presented a more complex picture. It was an area of lobular pneumonia considerably more extensive than the miliary lesions, and it contained areas of necrosing tissue. In some non-necrotic areas neutrophils predominated, and in the necrosing areas numerous identifiable neutrophils were seen as well as a considerable amount of nuclear "dust." In some areas within this lesion the inflammatory exudate consisted almost wholly of fibrin and monocytes, and a similar picture was present in the lung parenchyma which adjoined the lesion. In some areas the inner portion of the pleura was involved and the pleura covering the entire area was congested. Within the lesion the lung parenchyma and vessels could be identified in most areas. Several smaller vessels were involved in the acute inflammatory reaction and were possibly the source from which the generalized disease arose. Several structures having the appearance of bronchi were filled with leukocytes and were probably the principal source from which the disease process was being disseminated locally. There was no evidence of a peripheral zone of fibrous tissue. No "epithelioid" tubercles or giant cells were found.

The enlarged firm lymph node (Plate VIII, figure 27) showed widespread necrosis, and in numerous areas identifiable neutrophils were the predominant cellular element. The capsule of the lymph node was intact and it appeared that the tuberculous disease had not extended beyond the lymphoid tissue. The lymph nodes (Plate VIII, figure 28), with a gross appearance suggesting hyperplasia, showed on section numerous minute lesions in which neutrophils predominated. In a few of these lesions there was incipient necrosis, but in the majority there was no evidence of necrosis. These foci were almost all in the periphery of the nodes, and it seemed probable that they resulted from lymphatic rather than from blood-stream dissemination. In the various sections of lymph nodes no "epithelioid" tubercles or giant cells were found.

This case has been presented in some detail, as it evidently was a case of primary tuberculous infection of relatively short duration in a young infant. The pulmonary primary focus appeared to be a single lesion which had enlarged into a sizable area of lobular pneumonia which probably was caused in large measure by local endobronchial dissemination. This area of lobular pneumonia was composed of areas which differed in morphologic appearance and which would seem to be of different ages. The original minute focus was not apparent in the sections examined. The miliary pulmonary lesions closely resembled in structure experimentally produced lesions two or three weeks after an intravenous injection of virulent tubercle bacilli. The stage of necrosis observed in the lymph node which

lay in the path of drainage from the large parenchymal lesion corresponded with that which was consistently found in the experimental host four to five weeks after infection. Probably a focus which was at least as old as the necrosis in the lymph node was present in the large parenchymal lesion. As it appears that the disease in the infant was propagated from a single microscopic focus, perhaps two or three weeks more should be allowed for the development of the disease in the necrosing lymph node. On this basis it seems probable that the infection in the infant was approximately two months old. Failure to find any histologic tubercles or giant cells corresponds to the findings in a primary acute tuberculous infection with virulent bacilli in an experimental host.

The next earliest lesion, on morphologic grounds, was obtained from a white female who was sixty-one years old. She had been employed continuously for twenty-five years in the occupational therapy department of a tuberculosis hospital. Yearly chest roentgenograms had been obtained and were read as normal through 1949. In early March, 1950, the patient had the "grippe." Early in April she had her yearly routine chest roentgenogram, and this showed an extensive shadow in the outer portion of the right middle lobe. This was regarded as an acute pneumonic process, and she was given a course of treatment with penicillin. During a two-week period the pulmonary shadows did not change and the patient was admitted to the hospital.

The patient raised a scanty amount of sputum when first admitted to the hospital, and examination of a smear from a seventy-two-hour specimen for acid-fast bacilli was negative. Frequent roentgenograms during the ensuing six weeks showed an increase in the pulmonary shadows. Bronchoscopic examination showed only a slight amount of secretion in the middle lobe bronchus. Examination of a smear of bronchoscopic washings showed only a few neutrophils; no evidence of neoplastic tissue and no acid-fast bacilli were found. At this point a diagnosis of a malignant tumor of the lung was made, surgery was advised, and the right middle lobe was removed.

At operation the tissues of the upper and lower lobes were found to be normal, and no enlarged hilar or mediastinal lymph nodes were encountered.

Pathologic examination of the lobe showed a poorly defined firm mass which occupied the major portion of the lateral segment. The medial segment appeared to be free from any disease. No enlarged lymph nodes were found. Examination of a frozen section of a block of tissue from the outer and superior portions of the lateral segment showed the process to be tuberculous; however, examination of smears made from minced tissue failed to reveal any acid-fast bacilli. On section of the lobe after fixation, three poorly defined yellowish-gray necrotic lesions were found in the outer portion of the lobe, and the remainder of the disease presented the appearance of a pneumonic consolidation. No evidence of a neoplastic growth was found.

Microscopic study was made of sections from many areas of the resected lobe. Three separate necrotic areas of tuberculous pneumonia were found in the superior and outer portions of the lateral segment. One of these (Plate IX, figure 29) showed an organizing peripheral fibrotic zone. The necrotic zone had partly distintegrated, and a considerable infiltration of neutrophils was present in the broken-down areas. A communicating bronchus was covered by epithelium of the normal ciliated columnar type. The two other necrotic lesions showed little evidence of a fibrotic periphery, and the necrotic areas showed a partial disintegration of the dead pulmonary parenchyma. There were foci which were heavily infiltrated with neutrophils. One of these

lesions showed a bronchial connection which was similar to that already described. In none of the sections was there evidence of an old encapsulated necrotic lesion.

In the lung parenchyma in the region of the necrotic lesions, numerous "epithelioid" tubercles were present and giant cells were fairly common. Some of the tubercles showed an early fibrotic organization. All of the remaining portion (Plate IX, figure 30) of the disease was an extensive lobular pneumonia with little evidence of necrosis and without either tubercles or giant cells. In some areas the predominant cell was the neutrophil; in others, monocytes predominated; in still other areas, only lymphocytes were found, while in many areas there was a variable mixture of all of these cells.

Some of the alveoli were filled with necrotic material. Some of these microscopic necrotic foci were heavily infiltrated with lymphocytes, others with monocytes, and in still others there was no cellular infiltration. Several bronchial branches were filled with an exudate which consisted predominantly of neutrophils, and it seems probable that the minute necrotic foci in some of the alveoli represent a necrosis of the dispersed purulent bronchial exudate. Sections from several areas of the mesial segment of the lobe showed no evidence of disease.

It seems evident that the entire tuberculous process in this case was of fairly recent origin and that the large roentgenographic shadow represented a progressive endobronchial dissemination from relatively small, sloughing, necrotic pneumonic lesions. A feature of great interest was the absence of a significant amount of necrosis in the major and more recent pneumonic areas. This perhaps was related directly to the paucity of tubercle bacilli. Culture of the seventy-two-hour specimen of sputum obtained upon admission to the hospital yielded only two colonies of tubercle bacilli. Culture of subsequent samples of fasting gastric contents and of bronchoscopic washings showed no growth of bacilli, and culture of surgically excised tissue yielded only two colonies of tubercle bacilli. It required a prolonged search of many sections of tissue to demonstrate any bacilli and, when found, they were present singly in the necrotic lesions and in the purulent exudate within the bronchi. The extent of the pneumonic process would seem to be disproportionate to the number of bacilli found; however, the nature of the inflammatory reaction was in line with a paucity of bacilli.

In this case the major pathologic process was concerned with an early pneumonic lesion which had been instigated by a dispersion of debris from sloughing necrotic lesions. This had given rise to clinical "exudative" disease. The bacterial content of the necrotic lesions prior to necrosis was unknown, but at the time of examination the bacillary content was sparse.

In the experimental host it was found that the bacillary content was high prior to necrosis and low by the time necrosis became complete. Perhaps this was the condition encountered in the case under discussion. If so, then it would appear that the major inflammatory reaction was a response to the dispersed necrotic tissue rather than to the few bacilli which were present.

To the writer it seems reasonable to assume that the behavior of endobronchial disseminations is conditioned by the numbers of bacilli in the dispersed slough. If large numbers of bacilli are present, abscesses which soon become necrotic lesions are formed, and the resultant necrotic lesion may or may not liquefy

and slough at a later date. If bacilli are present in small numbers and are widely scattered, the pneumonic process may evolve into epithelioid tubercles which eventually heal completely by scar formation. If bacilli are rare or absent, the pneumonic process may resolve and leave a normal lung structure.

The next patient in point of age of disease was a four-year-old white male child who died from pulmonary tuberculosis after a known illness of approximately six months. Necropsy showed extensive pulmonary disease, numerous tuberculous ulcers in the ileum and cecum, and visible necrotic lesions in the spleen, liver, and kidney. There was no evidence of generalized miliary disease in the lung and no evidence of meningitis. Several enlarged necrotic hilar lymph nodes were present, but there was no macroscopic evidence that any of these had ulcerated through a bronchus. A large necrotic mass occupied the major portion of the posterior segment of the right upper lobe. It had a cross-sectional diameter of 4 cm. This mass was somewhat friable in portions, but there was no evident cavity formation. The remainder of the lobe was firm and airless, with only a few small recognizable necrotic foci. In the remainder of both lungs, numerous areas of disease contained many small lesions and had the irregular pattern of endobronchial, rather than the even distribution of a hematogenous, dissemination. Some of the small lesions were necrotic and others were not.

Microscopic study of the large necrotic mass (Plate X, figure 31) showed that no recognizable cellular elements were present in large areas, whereas in numerous focal areas there was a marked infiltration with neutrophils. In focal areas the lung framework had disintegrated, whereas in the remainder an intact dead lung framework was easily determined. Some of the interlobular septae were thickened by fibrous tissue. Such areas showed lymphocytic infiltration and normal patent vessels. Other interlobular septae were necrotic, although intact. This feature gave the large necrotic mass a somewhat lobulated appearance. There was a thin fibrotic zone peripheral to the necrotic mass, and in some areas sizable normal-appearing blood vessels were separated from the necrotic tissue only by a thin zone of fibrotic tissue.

The anterior segment of the lobe was occupied in large part by a tremendous number of "epithelioid" tubercles, and giant cells were numerous. There were only a few small necrotic foci. In some areas the tissue had the appearance of an organizing pneumonia. In other areas the alveoli were filled with a mixture of monocytes, lymphocytes, and neutrophils with no evidence of tubercles or giant cells.

Sections from other portions (Plate X, figure 32) of the lungs showed numerous clusters of small lesions. In some areas the majority of the lesions showed a necrotic central portion which was surrounded by a fibrotic zone; in other areas the majority of the lesions were "epithelioid" tubercles with and without giant cells and with and without evidence of fibrotic organization. In still other areas the lesions had the appearance of a recent focus of lobular pneumonia without evidence of "epithelioid" tubercles, giant cells, or necrosis. It appeared that endobronchial disseminations of different ages were present, some of which had proceeded to necrosis, whereas others had not.

Sections of the grossly necrotic lymph nodes showed that the peripheral fibrotic capsules were intact, and sections of other lymph nodes showed the presence of numerous "epithelioid" tubercles with and without giant cells.

In this case it was not possible to identify the original microscopic lesion which initiated the progressive primary infection. It appeared that, through

endobronchial dissemination, the major portion of the posterior segment of the right upper lobe became involved and that the large area of tuberculous pneumonia underwent necrosis prior to any liquefaction. Later, microscopic focal liquefaction had occurred which had resulted in sloughing and further extensive endobronchial dissemination. The dissimilarity in the behavior of the extensive although not massive endobronchial disseminations was of particular interest. The small foci which underwent necrosis showed the formation of a peripheral fibrotic zone, and those which had not necrosed apparently had proceeded to "epithelioid" tubercle and giant-cell formation. In some of the epithelioid tubercles there was evidence of fibrosis, so much so in some areas that the picture of an organizing lobular pneumonia was present.

The disease process found in the case under discussion resembled in most respects the morphologic picture seen in experimental animals which had survived six months or longer after a first infection. It is upon the basis of the time-sequence of events which was observed in the experimental studies that the case under discussion has been interpreted.

The fourth patient was a forty-five-year-old white male. Nine years previously a chest roentgenogram showed several dense shadows in the posterior portion of the left upper lung field and several linear densities in the superior and posterior portion of the right upper lobe. These were interpreted as "healed" pulmonary tuberculosis. Seven years later an increase was noted in the disease on the right. The size and density of these shadows continued to increase somewhat during the next six months, and the patient began to raise a small amount of mucopurulent sputum which was negative for tubercle bacilli on microscopy but was positive on culture.

The patient was hospitalized and was placed on a modified bed-rest regimen. During the next several months there was some recession of the roentgenographic shadows, which then remained stationary during a period of one year. A small amount of mucopurulent sputum continued to be raised. Laboratory examination on numerous occasions gave negative results for acid-fast bacilli on microscopy and occasional positive cultures with the growth of never more than a few colonies of tubercle bacilli. Roentgenographically, there was a question of cavity formation, and excision of the right upper lobe was advised and performed.

Macroscopic examination of the resected lobe showed that the diseased area was limited strictly to the upper portion of the posterior segment. There was no evidence of cavity formation; the tuberculous lesions were so arranged about an area of normal lung tissue, however, that cavity was suggested by the roentgenogram. There were three separate firm oval-shaped lesions, the largest of which measured 1.3 cm. in diameter. These lesions seemed to be well encapsulated, were rubbery in consistency, and were of a yellowish-gray color. There was no macroscopic evidence of calcification. The lesions lay close to the pleura. In direct connection with the inner portion of the largest necrotic lesion, there was another necrotic focus which seemed less well encapsulated by fibrous tissue. This focus measured 1.5 cm. across. In the same general region but not directly connected with the larger lesions, a number of smaller firm foci were present. Some of these were of a yellowish-gray color and others were of a grayish color.

All segmental bronchi appeared normal at point of origin. However, 2 cm. proximal to the largest focus, a branch of the posterior segmental bronchus showed a

thickened and congested mucosa and contained mucopurulent exudate. A thin wire probe inserted into this bronchus passed without hindrance into both the largest necrotic focus and the less well-encapsulated necrotic lesion.

Microscopic study of this lung showed that the three well-encapsulated necrotic lesions were of sufficient age so that numerous cholesterol crystals and small focal calcium deposits were present. Each of these lesions showed a well-preserved framework of dead lung tissue. The central portion of the largest lesion (Plate XI, figure 33) showed a slitlike opening, and in this area large numbers of acid-fast bacilli were found. No bacilli were seen in other areas of the lesion. One portion of another old necrotic focus contained masses of neutrophils, and in this region there was a communicating bronchus which was lined with stratified squamous epithelium. In this lesion the intact dead tissue was focally invaded by neutrophils. No acid-fast bacilli were found in sections of either this or the third old necrotic lesion.

Sections of the less well-circumscribed necrotic focus which was closely associated with the proximal portion of the largest old necrotic lesion (Plate XI, figure 34) showed an actively organizing fibrotic zone peripheral to the necrotic pneumonic lesion. The necrotic zone was heavily infiltrated with neutrophils in some areas, and here there was a partial disintegration of the parenchymal framework. This lesion would appear to be of much more recent origin than the three other necrotic foci. Acid-fast bacilli were present in large numbers in focal areas and were not found in the major portion of the necrotic zone.

Examination of the smaller lesions which were not directly associated with the larger ones showed that some were necrotic and some were "epithelioid" tubercles with a variable number of giant cells. An occasional small parenchymal scar was found, a few of which were in areas of the posterior segment which macroscopically appeared to be normal.

Sections of the bronchial branches which were closely associated with the large lesions showed that some had a marked lymphocytic infiltration and congestion of the mucosa without any evidence of ulceration. A few "epithelioid" tubercles and giant cells were also present in the mucosa and there was a purulent exudate in the lumen. One bronchial branch showed complete necrosis of the mucosa and submucosa. All of the other bronchi presented a normal appearance.

In this case it is evident that the endobronchial disseminations manifested by an increase in the roentgenographic shadows were related directly to old necrotic lesions which had been present for at least nine years prior to the time of surgery. Evidently the sloughing from these lesions was from focal areas of liquefaction, for there was no macroscopic evidence of cavity formation. The endobronchial disseminations were limited to the posterior segment. Some had proceeded to necrosis, others had formed non-necrotic "tubercles," and some of these latter lesions had healed completely by scar formation.

The final lesion was from a seventeen-year-old high school girl whose first chest roentgenogram was taken in the course of a school survey. This roentgenogram showed a round density, 2 cm. in diameter, in the region of the right clavicle and a less dense shadow which extended to the apex of the lung. No tubercle bacilli were cultured from the fasting gastric contents, and the patient raised no sputum. Approximately two months later the lesion was excised. Streptomycin–PAS therapy had been instituted a few days prior to surgery. At operation the only lesions found

were in the area indicated in the roentgenogram of the chest, and the apical segment of the right upper lobe was removed. The portion of lung tissue removed measured 3.5 by 3.0 by 2.5 cm. over all.

A small bronchus in the resected surface appeared normal; near the largest lesion, however, this bronchus showed a thickened wall and was occluded by a yellowish-gray soft plug. A fine wire probe inserted into this area passed easily into the lesion. The largest lesion was firm, roughly spherical, and measured approximately 2 cm. in diameter. Extensive calcification was found on section. The lesion was of a rubbery consistency with some focal areas which were friable. It was well encapsulated and did not have the appearance of a filled-in cavity. Adjacent and distal to this large lesion there were other focal firm areas, the largest having a diameter of 7 mm. No evidence of calcification was found in these smaller foci which varied in color from a pearly-gray to a yellowish-gray. The largest of these lesions had a central portion which had the consistency of thick cream.

Microscopic study of the largest lesion (Plate XII, figure 35) showed an intact dead lung framework in most areas, although there were foci of an amorphous granular nature. In one area a piece of dead cartilage was found, and in another portion there was a bony metaplasia with the presence of bone marrow in the outer portion of an area of dense calcification. Two bronchi consisting of a necrotic granular center and a fibrotic periphery extended peripherally through the fibrotic capsule.

The second largest lesion (Plate XII, figure 36) showed a well-formed periphery of fibrous tissue and a necrotic central portion which was heavily infiltrated with neutrophils in some areas. There were also quite a few smaller lobular pneumonic foci. Some of these had undergone necrosis, others were small clusters of "epithelioid" tubercles with and without giant cells, and an occasional lesion was a fairly recent area of lobular pneumonia without either necrosis or tubercle formation. An occasional small parenchymal scar was present.

The morphologic complexity of the tuberculous disease clearly indicated that in part it was ancient and in part it was of recent origin. It takes a number of years for bony metaplasia to develop in the periphery of a calcified tuberculous lesion, but the writer is unable to state the number of years that must elapse. Since the proximal bronchus contained easily removable necrotic debris, the ancient lesion could not be considered to be completely sealed off. Other bronchi in a similar condition extended through the distal portion of the fibrotic capsule. It seems probable that these bronchi were the source from which the more recent disease had its origin. The morphologic features of the active spreading disease in this case closely resemble the picture described in the preceding case. The presence of an ancient large necrotic pneumonic lesion suggests the potential hazard of such lesions even after considerable calcification and bony metaplasia have developed.

GENERAL COMMENT

These 5 cases have been presented in some detail, for, with the exception of cavity formation, they illustrate all of the complex morphologic features which are to be found in progressive human pulmonary tuberculosis. It is evident that the age of the disease process is not necessarily related to the age of the patient.

The sixty-one-year-old female who had worked in a tuberculosis hospital for twenty-five years had a progressive tuberculosis which was probably of shorter duration than that found in the four-year-old boy who died from the disease. The essential morphologic features in the two were similar; however, in the older person, the major portion of the disease was composed of such recent areas of lobular pneumonia that neither "epithelioid" tubercles nor giant cells had had time to form. The seventeen-year-old girl showed the disease of greatest age, and the sixteen-month-old infant showed the disease of shortest duration.

Evidence of endobronchial dissemination was found in each case, and in no instance was it evident that a tuberculous lymph node was the source from which the progressive pulmonary disease had its origin. The dominant morphologic feature in the infant was abscess formation, and it was evident that death occurred before the abscesses had proceeded either to liquefaction and sloughing or to complete necrosis without sloughing. In the 4 other cases the disease was of longer duration and was composed of necrotic and non-necrotic components. Focal liquefaction and sloughing of a necrotic component into a connecting bronchus were the sources from which the early non-necrotic pneumonic component had its origin. The subsequent behavior of the fresh pneumonic lesion would seem to be related to the quantity of tubercle bacilli which were brought into the area with the dispersed bronchial secretions.

The lobular pneumonia may proceed through early abscess formation to complete necrosis; it may evolve into numerous "epithelioid" tubercles and giant cells without any significant necrosis; it may completely resolve; or, more commonly, all three of these processes may occur in variable proportions. Dynamically, the necrotic lesion represents the unfavorable phase of the disease. It is difficult to dispose of, it is the chief harborer of bacilli, and too often it displays a tendency to liquefy and slough. On the other hand, the non-necrotic tubercle eventually heals completely by scar formation, and the area in which complete resolution has occurred reveals a normal lung structure. These features will be presented in greater detail in the following chapter. On this basis, tuberculous disease may be considered to be composed of a necrotic and of a non-necrotic component which, from roentgenographic shadows, can hardly be differentiated one from the other.

PLATES VIII–XII follow

PLATE VIII

FIG. 25. (× 15) White female, age sixteen months. Case discussed in text. Illustration shows the spreading primary parenchymal lesion which was an open focus of lobular pneumonia. There is no evidence of an "encapsulation"; neither are there "epithelioid" tubercles or giant cells. Liquefaction of some portions of the lung framework is underway and necrosis also is taking place. To the right a sizable blood vessel is directly involved in the tuberculous process. Directly below the vessel the circular area which is largely filled with purulent exudate is a bronchus. This situation indicates the way in which the lesion has attained its size. The entire lesion may be regarded as a tuberculous abscess which simultaneously is undergoing enlargement through endobronchial dissemination, liquefaction, and necrosis. This process is a forerunner of cavity formation.

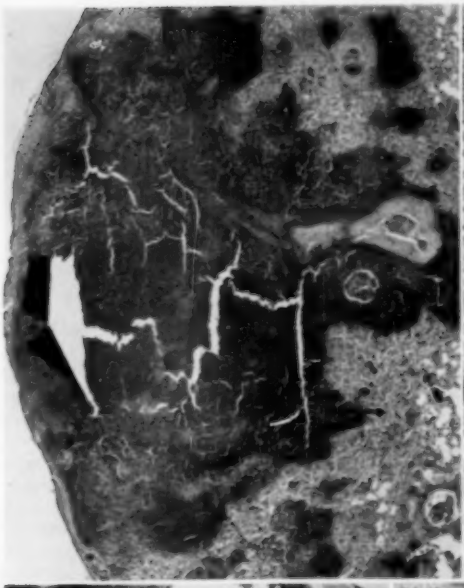
FIG. 26. (× 15) Same patient as above. Illustration shows the general picture of the hematogenous miliary tuberculosis. All of these lesions are small open foci of lobular pneumonia. The blue color is due to a predominance of neutrophils. These lesions are minute miliary abscesses. Note in the largest lesion to the right the red tinge at the periphery. This is the beginning of the process of necrosis. No "epithelioid" tubercles or giant cells are present.

FIG. 27. (× 15) Same patient as above. Section of lymph node in line of drainage from primary parenchymal focus shown in figure 25. The entire lymph node is involved, and the process of necrosis is more advanced than in the parenchymal focus. In areas in which cells can still be identified, the predominant cell is the neutrophil.

FIG. 28. (× 15) Same patient as above. Section of hyperplastic lymph nodes. There are numerous miliary abscesses. In some of these necrosis is underway. These miliary abscesses may have resulted from either lymphogenous or hematogenous dissemination or from both sources.

The pathologic changes in this case are not unlike those found in a first infection in rabbits up to one month after infection.

Fig. 25



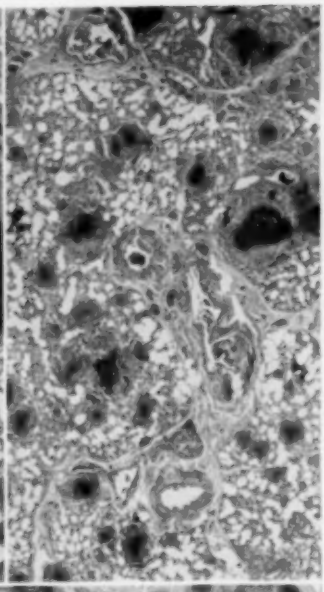


Fig. 26

Fig. 27

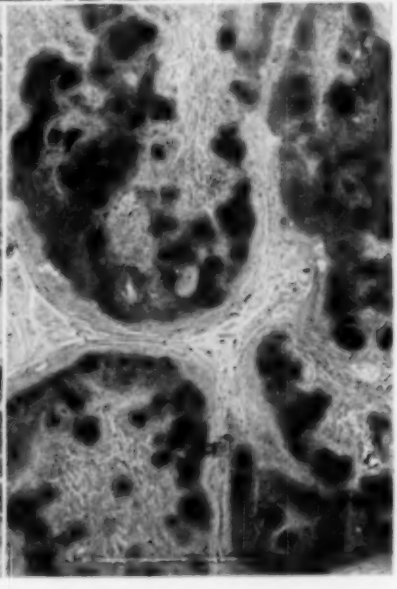


Fig. 28

PLATE VIII

PLATE IX

FIG. 29. (× 15) White female, age sixty-one. Discussed in text. Note the cellular fibrotic zone about the periphery of the large necrotic lesion. This, on morphologic grounds, was the oldest lesion found. To the right is the connecting bronchus which is largely filled with necrotic debris and purulent exudate. The wall of the bronchus is necrotic near the lesion, and there is an intact normal epithelial lining of the bronchial wall furthest to the right. Bluish areas in necrotic zone are due to heavy infiltration with neutrophils. In large part the dead lung structure is intact. This bronchus is the source from which the dispersion of the disease occurred. Note the numerous "tubercles" and giant cells above and below the bronchus. These are endobronchial disseminations and already show considerable fibrosis.

FIG. 30 (× 15) Same patient as above. Illustration is from an area of the lobe near the hilum. The lesion is an area of lobular pneumonia in which the lung framework is viable and intact. There are no "epithelioid" tubercles or giant cells. In some alveoli there are small areas of necrotic debris which in all probability represent bits of dispersed purulent exudate which has undergone necrosis. The cellular components are a variable mixture of lymphocytes, monocytes, and neutrophils. It seems probable that in time numerous "tubercles" and giant cells similar to those present in figure 29 would have been formed in this lesion. In some areas there was a considerable deposit of fibrin. Tubercle bacilli were extremely difficult to demonstrate. To the writer it appears that the major inflammatory reaction can be attributed to the presence of necrotic debris which has been carried into the area rather than considered as a reaction to the infectious agent itself. There is small likelihood that a lesion of this nature would become a necrotic lesion such as is shown in figure 29.

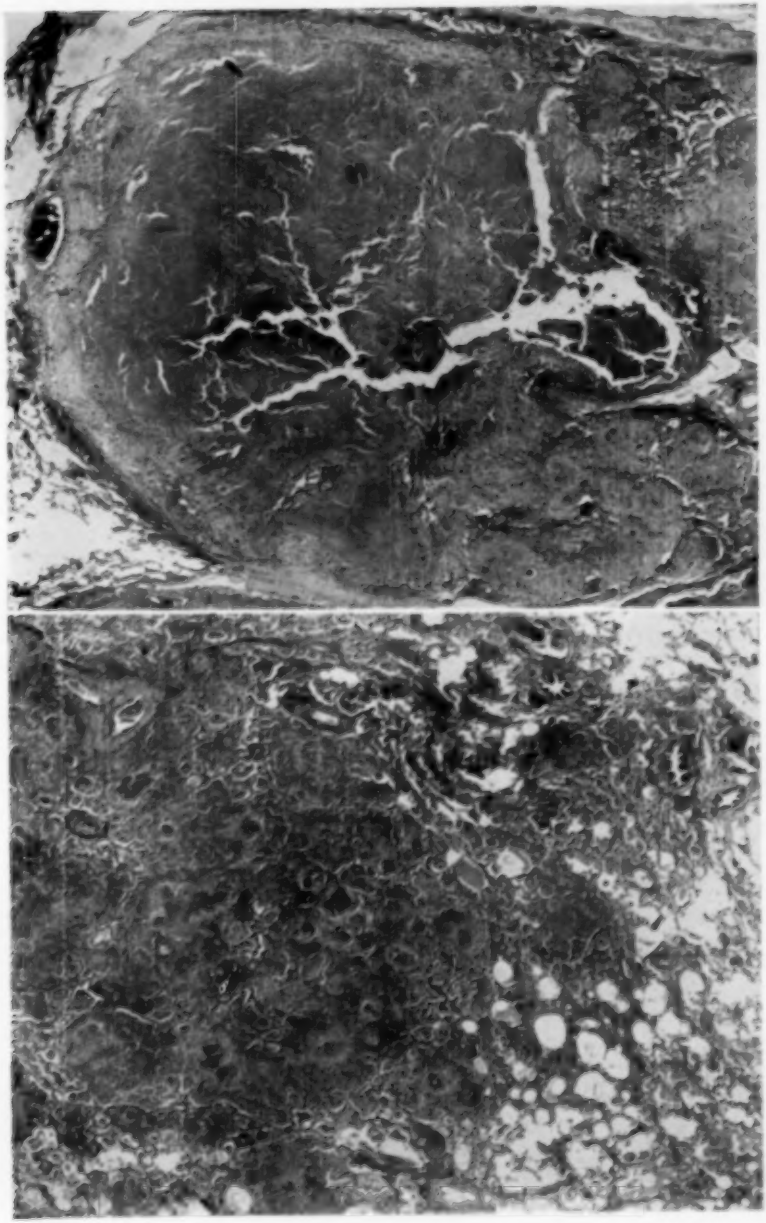


FIG. 29

FIG. 30

PLATE IX

PLATE X

FIG. 31 (× 1.5) White male, age four years. Discussed in text. Section through right upper lobe. The large necrotic lesion occupies the major portion of the posterior and apical segments. In large areas the dead lung framework is absent and in other large areas it is intact. The blue color present in the necrotic lesion is due to heavy infiltration with neutrophils. Note the relatively thin zone of fibrotic tissue which separates the living from the dead tissue.

The anterior segment (left upper quadrant) is largely occupied by "epithelioid" tubercles, and giant cells are numerous. There is little evidence of necrosis. In considerable areas the structure is that of an organizing pneumonia.

FIG. 32. (× 1.5) Same patient as above. Section from opposite lung. This is typical of all lung tissue except the right upper lobe. Because of an irregularity of distribution and a considerable variability in size, the lesions are interpreted as endobronchial rather than hematogenous disseminations. There is a considerable difference in the amount of necrosis in different lesions, and this is taken to indicate that endobronchial disseminations of different ages are present. The red areas are the necrotic foci. Note the several small necrotic foci in the two lymph nodes in the bottom portion of the illustration. These would seem to represent lesions induced by lymphatic drainage from the parenchymal lobular pneumonic foci.

FIG. 31

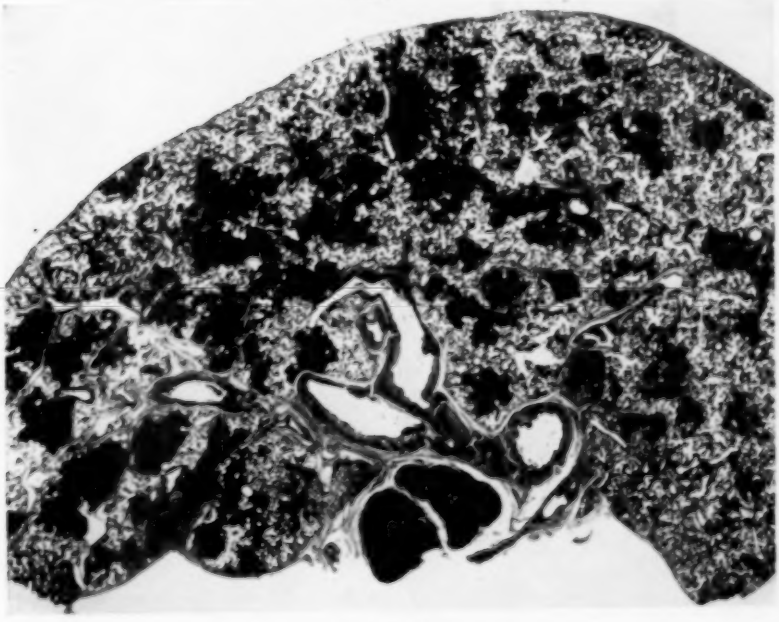


FIG. 32

PLATE X

PLATE XI

FIG. 33 (× 3) White male, age forty-five. Case discussed in text. The large necrotic lesion shows a thin periphery of viable fibrotic tissue and a considerable zone of dead fibrotic tissue. Inside the latter an intact dead parenchymal framework is present. There is no evidence of calcification, but numerous cholesterol crystals are present. In the dead tissue adjacent to the slitlike central opening, tubercle bacilli in colony formation were found. The necrotic focus below the large lesion is of lesser age than the large one, and the necrotic pneumonic area in the upper left-hand quadrant is of still more recent origin. There are several separate groups of "tubercles." These various lesions are all regarded as endobronchial disseminations. The numerous minute blue dots are collections of lymphocytes.

In the left lower quadrant the round lesion is a bronchus which contains necrotic debris and has marked necrotic endobronchial disease. The two bronchi to the left contain purulent exudate which is intermixed with bits of necrotic debris.

FIG. 34. (× 3) Same patient as above. Section approximately 1.5 cm. nearer the hilum of the lobe. The two sizable necrotic lesions to the right are similar in character to the large one in figure 33. The lower one of the two shows considerable liquefaction with a heavy infiltration of neutrophils. In another section a small area of the inner surface of the fibrotic "capsule" at the bottom of the lesion had a lining of stratified squamous epithelium. Acid-fast bacilli were not found in the search of sections of both lesions at two different levels.

The large pneumonic lesion in the lower left-hand quadrant is undergoing necrosis, and its fibrotic "capsule" is in process of developing. The blue color of this lesion is due to heavy infiltration of neutrophils. Bacilli in large numbers were found in the tissue in the region of the slitlike cracks and were not found in other portions. The three bronchi above this lesion show marked lymphocytic infiltration, congestion and edema of the mucosa, and have an intact normal epithelial lining. An occasional "epithelioid" tubercle and giant cell also are present in the mucosa. This is the most common of all bronchial disease in tuberculosis. The numerous, scattered small blue dots are collections of lymphocytes.

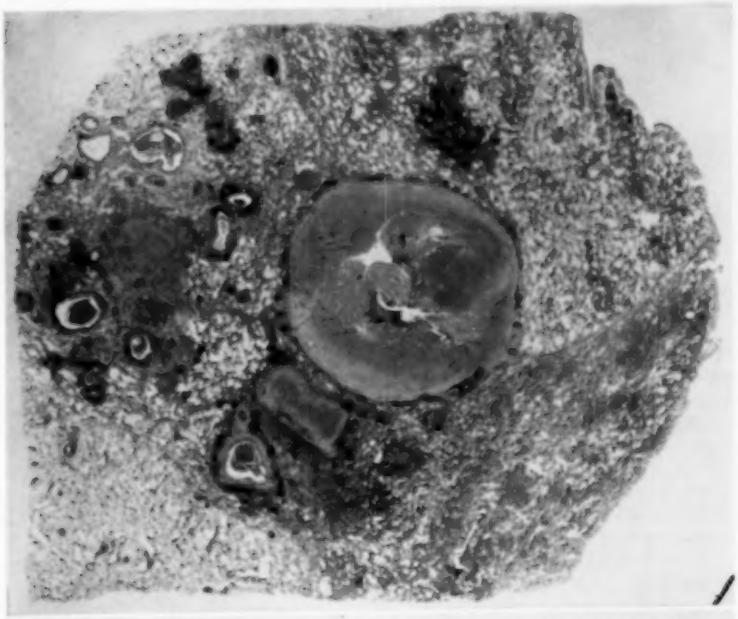


FIG. 33

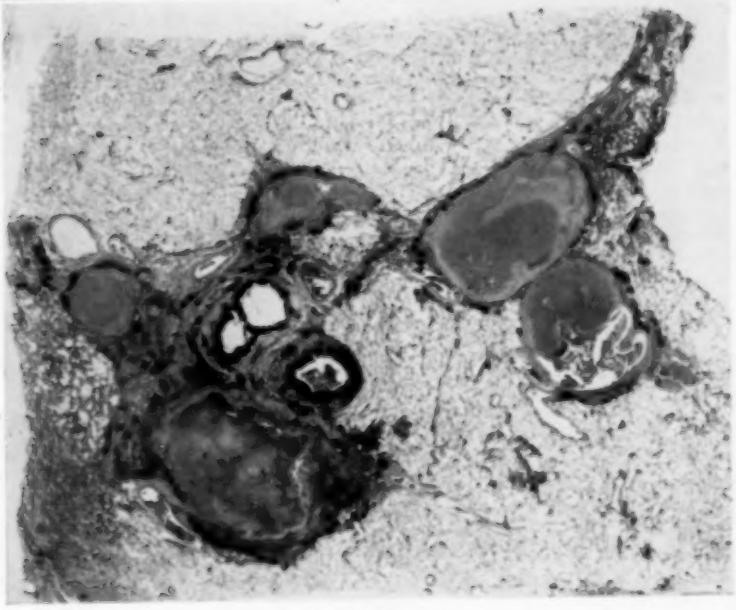


FIG. 34

PLATE XI

PLATE XII

FIG. 35. (× 5) White female, age seventeen. Case discussed in text. Section from large old necrotic lesion. Tissue had to be decalcified for thirty-six hours before it could be sectioned. In the periphery of the necrotic tissue in the left lower quadrant, several small areas of bony metaplasia with bone marrow present were found. This large lesion appeared to be composed of several areas of lobular necrotic tuberculous pneumonia which seemed to be of different ages, for some had well-formed necrotic fibrotic peripheries within the lesion as a whole and there was a difference in the density of the calcification. In the region of the breaks inside the lesion there was no lung framework, whereas in other areas the dead lung framework was easily identified.

The projection (lower right-hand quadrant) beyond the large lesion showed no calcification and appeared to be a bronchus which was filled with necrotic debris. Adjacent to the slitlike area that leads down to this projection, a small piece of cartilage was found in another section. This definitely identifies the course of the bronchus.

Note the several small pneumonic lesions in the tissue to the right. There are aggregates of "epithelioid" tubercles which indicate endobronchial disseminations of fairly recent origin.

No tubercle bacilli were found in a thorough search of sections from three different levels of the large lesion.

FIG. 36. (× 3) Same patient as above. Section from just beneath the pleura. The fact that there were some recent deposits of calcium (lower right quadrant) in the small part of the lesion was not appreciated prior to staining of the sections. This large lesion was peripheral and adjacent to the one shown in figure 35. It would appear to be of much more recent origin since there was no macroscopic evidence of calcification. It is regarded as an endobronchial extension from the old lesion. This lesion contained soft creamy pus, and large numbers of acid-fast bacilli were present. The bluish areas in the necrotic tissue are ones in which there was a heavy infiltration with neutrophils.

The numerous lesions peripheral to the large lesion represent endobronchial disseminations of fairly recent origin. They are largely composed of "epithelioid" tubercles and giant cells. A few recent necrotic lesions are also present. A few small lobular pneumonic foci were found in which there was neither tubercle formation nor giant cells.

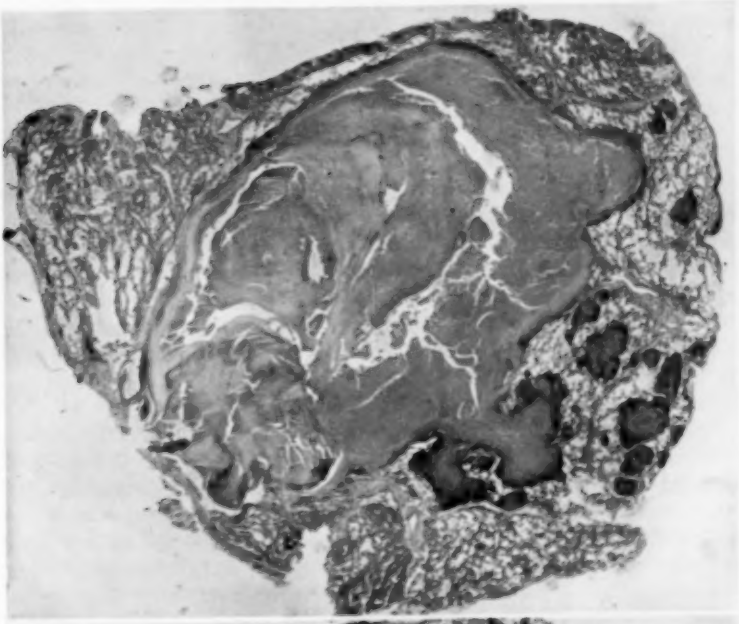


FIG. 35

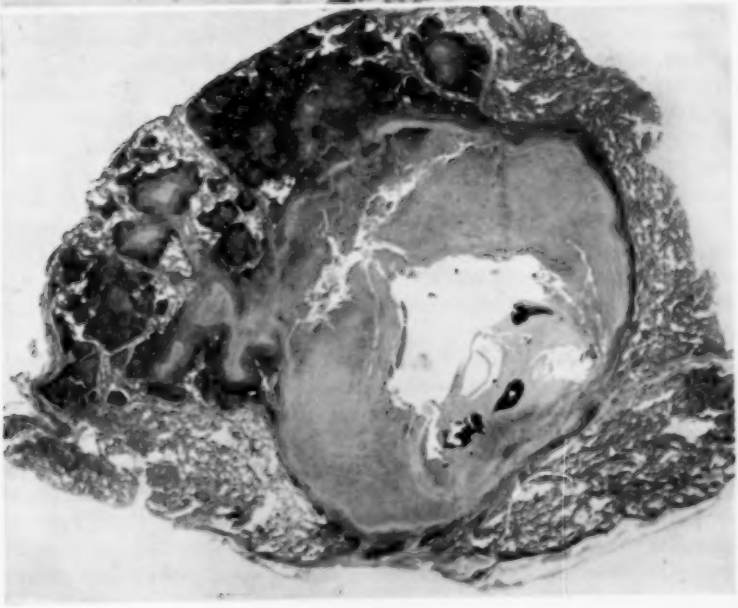


FIG. 36

PLATE XII

CHAPTER V

BEHAVIOR OF THE PARENCHYMAL TUBERCULOUS LESION

Pulmonary alveoli represent the ultimate endings of bronchi. Consequently, parenchymal and bronchial disease in progressive pulmonary tuberculosis are inextricably bound together. On the other hand, the pulmonary vascular system has little to do with the dissemination of the disease within the lung except in generalized hematogenous tuberculosis, which occurs relatively seldom, and in the endobronchial dissemination which is occasionally associated with hemorrhage from tuberculous cavities. Fortunately, vascular involvement in areas of necrosing tuberculosis leads in most instances to thrombosis with organization of the thrombus peripheral to the pneumonic lesion.

The lymphatic system also plays a minor role in progressive pulmonary tuberculosis. Although tubercle bacilli often gain access to lymph vessels, they are carried by the lymph current to lymph nodes, where they are filtered out. The tuberculous infection of the lymph node may progress no further than the formation of epithelioid tubercles which eventually heal and leave a scar of microscopic proportions. On the other hand, the lymph node infection may proceed to a necrotic lesion which may involve the entire node. After necrosis has occurred, a peripheral zone of scar tissue usually is laid down which in most instances effectively seals off the lesion. On occasion the disease may extend beyond the confines of the lymph node, and adjacent bronchi and vessels may become involved. If such a lesion should undergo liquefaction and slough, then disastrous results may ensue. Erosion of a bronchial wall and sloughing of the liquefied contents may be followed by massive endobronchial dissemination. Erosion of both a bronchial wall and an adjacent large vessel may lead to a sudden and fatal hemorrhage. Erosion into a large vascular branch may cause an overwhelming generalized miliary tuberculosis. Although such results are dramatic, fortunately they are uncommon. In the writer's necropsy study of cases of sudden and unexpected death, it was apparent that, in large measure, the tuberculous infection of pulmonary lymph nodes is a rather innocuous affair, even in persons who had succumbed to extensive pulmonary disease.

The dynamics of pulmonary tuberculosis is a function of the behavior of the disease in the parenchyma as well as in the bronchi. In a discussion of the behavior of these lesions, it seems best to consider the parenchymal and bronchial components separately, keeping in mind that this separation is entirely artificial.

To attempt to present a coherent description of the behavior of the parenchymal tuberculous lesion based only on a study of human disease would resemble taking a carefully charted voyage on a rudderless boat. The rudder, which the writer has chosen to use as a guide through the complex morphologic features of these lesions, is the time-sequence of events which was observed in the study of experimentally produced pulmonary tuberculosis.

The initial parenchymal lesion is a microscopic focus of lobular pneumonia. The behavior of this lesion is determined in large measure by the ability of the tubercle bacillus to reproduce and to maintain its reproduction and by the forces which the host employs to overcome or to check the growth of the parasite. In this process the initial number of bacilli is not the deciding factor.

The least complicated process in the interplay between the forces of the host and the parasite is the fairly prompt destruction of the parasite and a healing of the lesion by resolution.

A somewhat more complex process is the formation of the histologic "epithelioid" tubercle. Here the parasite is less easily destroyed, but eventually the lesion heals completely by scar formation.

A still more complex process evolves if the parasite succeeds in reproducing in considerable numbers. In this instance the reaction of the host leads at first to the early phase of abscess formation in which neutrophils predominate and later to the initiation of a process which induces almost simultaneously a complete necrosis of the lesion and a lysis of bacilli. If all bacilli in a small necrotic focus are destroyed in this process, the lesion slowly heals by a combined process of fibrosis and calcification. Ancient lesions of this type not infrequently show a metaplasia to bone and bone-marrow formation. This battle scar persists indefinitely and is found commonly in the lungs of human beings who have never had "clinical" tuberculosis. These different types of behavior are observed in *initial* lesions which are too small to be recognized in chest roentgenograms.

A different behavior of the *initial* necrotic lesion may occur in the human lung, particularly if the focus is located in the superior and posterior portions of a lobe. A liquefaction and sloughing of some or all of the necrotic contents of the small lesion may take place and, if the bacilli have not been destroyed, viable bacilli in variable numbers are carried along with the slough. The dispersion of the sloughing material into new areas of the parenchyma places the host in the position of having to dispose of both the parasites and the host's own necrotic tissue. This is always the situation when the disease has progressed sufficiently to become manifest roentgenographically and clinically. By the time the pathologist has the opportunity to study the disease process, multiple lesions of different size, of different age, and of different morphologic appearance have developed.

From the experience gained from the study of necropsy and of surgically resected tuberculous pulmonary tissue, backed by a considerable study of experimentally produced tuberculosis, the writer will attempt to delineate the behavior of the parenchymal disease. This description is tempered to a degree by experience gained from regular attendance at clinical conferences at which, time after time, the unpredictability of the behavior of the disease, as revealed in roentgenographic shadows, was observed.

The main theme of this discussion will be to record *how* the parenchymal lesions may behave. To the writer, a knowledge of the *why* of behavior is too meager to permit more than a suggestion, here and there, of a possibility. All of the parenchymal lesions under consideration are areas of lobular pneumonia of larger or smaller size which follow the dispersion of necrotic debris through

bronchi which drain sloughing necrotic lesions. The early beginnings of these endobronchial disseminations seldom are observed; however, it would appear that their behavior is conditioned by the amount of dispersed necrotic material and the numbers of bacilli in the necrotic debris. On occasion the writer has observed in surgically resected tissue an area of lung parenchyma in which alveoli (Plate XIII, figure 37) were filled with necrotic debris, with the alveolar walls within the area presenting a normal appearance. This may well be an artifact due to surgical manipulation, but it serves to illustrate a condition which probably is a frequent beginning of new parenchymal foci.

The dissemination of the sloughing debris through bronchi results in pneumonic lesions which appear to differ considerably in their subsequent behavior. The ensuing morphologic changes may be either those of resolution, of tubercle formation, or of necrosis. It is probable that all three processes occur to a variable degree in all pneumonic disseminations. To facilitate discussion the pneumonic lesion is divided into the non-necrotic or favorable component and the necrotic or unfavorable component.

THE NON-NECROTIC COMPONENT

Although an abundance of material can be had from necropsy specimens for a study of the inflammatory response in recent pneumonic lesions, such material is not suitable because, commonly, bacteria other than tubercle bacilli can be grown from the lesions. This situation is not surprising, for most tuberculous patients usually are in a debilitated state for a long time prior to death and bronchial cleansing is greatly impaired. Resected tissues are satisfactory for study because they rarely, in the writer's experience, contain bacteria other than tubercle bacilli. However, it is uncommon to find recent pneumonic lesions in resected specimens. This presumably is a consequence of the considerable chemotherapy customarily administered prior to surgery.

The best specimen the writer has seen for the study of a recent pneumonic process was in the case of the sixty-one-year-old woman reported in Chapter IV. For the details of this lesion, the reader is referred to this description. The mixed cellular response and the extreme paucity of bacilli in the fresh pneumonic lesion in this case suggest that the inflammatory reaction was due in large part to the presence of the patient's own necrotic tissue. It is probable that this pneumonic lesion would, to a great extent, have healed, in time, by resolution. However, the oldest portion of the pneumonic process consisted of histologic "epithelioid" tubercles which, in the writer's opinion, would not heal by resolution. Roentgenographic evidence showed that the lesion had been present for more than two months and that it had slowly increased in size. From this, one may surmise that it takes time, perhaps a few weeks, for well-developed histologic tubercles to form.

The next subject for consideration is the behavior of the "epithelioid" or histologic tubercle and the associated giant cells. The writer was taught that these structures represented the early tuberculous lesion; that they were specific for the disease; and that, if tubercle bacilli were present, here was the place to find

them. He has long since discarded these notions. He recognizes that the association of tubercles and giant cells is a valuable diagnostic aid to the pathologist, as this association is found more frequently in tuberculosis than in any other disease except, perhaps, in sarcoidosis. Because the "tubercle" has been regarded for so long as the focal point around which the remainder of the disease process revolves, the observations which led the writer to discard this concept will be summarized.

Thousands of giant cells in various tissues have been searched for acid-fast bacilli. On a rare occasion one or two bacilli have been seen. This was not due to a faulty staining technique because acid-fast bacilli were found frequently in other lesions in the same slide. Giant cells have been observed free within alveoli as well as intermingled with tissue. Not uncommonly anthracotic pigment was observed, sometimes in considerable amount, in association with the nuclei in the outer portion of a giant cell. This suggested that so-called "alveolar" phagocytes which had already phagocytosed pigment had later become a part of the giant cell. Reconstruction of giant cells from serial sections revealed a variation from a spheroid mass with a diameter of 30 micra to a long-pronged structure with greatest dimensions of 100 by 600 micra. Such large structures appeared as a single large giant cell in one section and as three or four separate giant cells at another level. On rare occasions in the study of giant cells in experimentally produced tuberculosis, the writer found a single mitotic figure among the numerous nuclei of a giant cell. This mitigates against these structures being living homogeneous units such as multinucleated tumor giant cells. If cells of this latter type undergo mitosis, all nuclei participate.

These along with less significant features indicate to the writer that the giant cell in tuberculosis is merely a foreign-body giant cell, with the foreign body being a bit of dead tissue. The giant cell harbors tubercle bacilli only rarely and disappears with complete healing of the lesion.

Large numbers, perhaps thousands, of "epithelioid" tubercles have been studied to determine whether any evidence could be found to indicate a considerable increase of tubercle bacilli and whether an enlarging necrotic lesion might result from a growing tubercle. In most lesions no bacilli were found and, when they were found, there were only a few single bacilli which either had been phagocytosed by epithelioid cells or lay free in the tissue. In no instance were groups of bacilli found which would suggest either active intracellular or extracellular multiplication. It would seem that in lesions of this type few bacilli were present and these succeeded in multiplying only to a slight degree; apparently the environs were not conducive to a continuous and rapid increase in the bacillary population.

In no instance was evidence found which would support the proposition that a "tubercle" was growing. The writer has been unable to find a necrotic focus of substantial size which was surrounded by epithelioid tubercles. A lesion of this structure would be a prerequisite as evidence of growth of a tubercle. There is some variation within narrow limits in the size of the small necrotic area which not infrequently is present within a tubercle; however, this probably represents

a condition which was present prior to tubercle formation. On the other hand, it has not been difficult to find evidence of fibrotic organization of tubercles. In some instances, small epithelioid tubercles without either giant cells, evidence of necrosis, or evidence of fibrosis were found adjoining a tubercle with considerable fibrosis. This new tubercle may have arisen from the emigration to the area of an epithelioid cell (monocyte) with a phagocytosed tubercle bacillus.

On occasion, evidence was found which indicated that lesions which were composed in large part of tubercles could persist for a long time. One such specimen was obtained from a necropsy on a tuberculous patient who died from causes other than tuberculosis. This patient had never received chemotherapy. An area of new disease was noted four years prior to his death. During a period of one year there was some clearing of the roentgenographic shadow, but during the ensuing three years no significant change was noted. A histologic study of this area of disease (Plate XIII, figure 38) showed that it was composed predominantly of epithelioid tubercles but that there were also a few necrotic lesions. A few of the tubercles showed no evidence of fibrosis, and these would seem to have been of fairly recent origin. The remaining portion of the lesion showed tubercles with varying degrees of fibrotic organization and areas of scar tissue only. These latter areas were regarded as completely healed tubercles. No bacilli were found in a thorough search of two levels of the lesion. Failure to find bacilli was taken to indicate only that the bacillary population was sparse.

A somewhat similar situation was found in tissue resected from a nurse who, during a period of twelve years, had had several relapses. The last relapse showed an increase of roentgenographic shadows on the left side and no change on the right. The area of disease on the right had shown no significant roentgenographic changes during the previous five years. Shortly after the increase of disease in the left lung was found, streptomycin-PAS therapy was begun. Three weeks later resection of the disease on the right was performed, and five months later the diseased tissue in the left lung was removed. Microscopic study of the specimen removed from the right lung (Plate XIII, figure 39) showed a morphologic picture similar to that described above in the necropsy specimen except that larger and more numerous necrotic lesions were present. Histologic study of the specimen from the left side showed only scars and necrotic lesions. Extensive clearing of roentgenographic shadows on the left occurred during the five months of chemotherapy.

It was unusual to find more than an occasional tubercle in resected specimens, provided the patient had received chemotherapy for four months or longer prior to resection. In all resected specimens some parenchymal scars were found irrespective of the length of chemotherapy. In some cases parenchymal scarring was the dominant feature (Plate XIII, figure 40); however, in only 3 of the 295 tuberculous patients from whom pulmonary tissue was resected was there an absence of necrotic lesions of macroscopic proportions.

Parenchymal scarring was also a frequent finding in necropsies on tuberculous patients who had never received chemotherapy. In the necropsy specimens the amount of parenchymal scarring varied from slight to extensive. The extensive

scars were not related to a healing of a tuberculous cavity because there were bronchial and vascular branches and scattered small foci of alveoli throughout the area. Scars which represent healed cavities contain no elements of normal lung structure.

These scarred areas, both in the necropsy and resected specimens, indicate to the writer that non-necrotic areas of tuberculous pneumonia of varied sizes had healed completely by fibrotic organization rather than by resolution. It seems probable from all available evidence that at some stage the morphologic picture would have been one of "tubercles."

From the evidence which has been gleaned from a considerable study, it would appear that the histologic tubercle represents, to a large degree, a lesion in which there is an even balance between the tubercle bacillus and the host. Although in some instances this balance may continue for an indefinite period, the host sooner or later wins out and the lesion heals completely. It may be that tubercles can be formed without the presence of bacilli, but this would be impossible to prove in a study of human tissues. The residual scars affect to a greater or lesser extent a normal function of the lung. It is in association with these scars that obstructive emphysema (Plate XIV, figure 41) and bullae develop. The scars do not harbor bacilli which could later cause a relapse of the disease. On this basis, tubercle formation represents a favorable aspect of the disease.

THE NECROTIC LESION

In the experimental animal it was found that local enlargement of a tuberculous lesion occurred prior to necrosis. This was due to a spilling of the inflammatory cellular infiltrate into adjoining alveoli through bronchioles and from early ulceration of bronchi. A situation analogous to this, which has been discussed in Chapter IV, was found in the lung of a sixteen-month-old infant. In experimentally produced pulmonary tuberculosis, complete necrosis of a lesion was found to occur between the fourth and sixth weeks in a first infection. In reinfection, necrosis may occur within two weeks. However, only a few minute necrotic foci were observed. The necrosis occurred prior to the formation of a peripheral fibrotic zone. Liquefaction after necrosis required several months, and during the process of liquefaction there was a reinvasion of neutrophils.

In the study of necropsy material from tuberculous patients, the writer has seen on several occasions areas of lobular pneumonia which both macroscopically and microscopically had the appearance of an acute nontuberculous infection. Acid-fast stains of these lesions showed large numbers of tubercle bacilli in some and none in others. As a variety of microorganisms other than the tubercle bacillus frequently can be grown from acute pneumonic lesions found in a tuberculous lung at necropsy, it would seem that the only way to determine the nature of the lesion would be the demonstration of the type of infectious agent in an individual lesion. In the lesions which contained large numbers of tubercle bacilli, the cellular content was composed predominantly of neutrophils. In the experimental animal, it was lesions of this structure which underwent necrosis.

On occasion the writer has observed necrosing and necrotic lesions without any peripheral fibrotic zone in pulmonary tuberculosis in man. Lesions of this type have been found most often in tuberculous patients whose clinical course of disease has been of relatively short duration. In a pulmonary lobe which was resected on the basis of a clinical diagnosis of carcinoma, a solid firm lesion which measured 5 cm. on cross-section was found. Microscopic study showed the lesion to be composed in part of an acute pneumonic lesion in which the predominant cellular reaction was one of neutrophils and, in part, of pneumonia which was undergoing necrosis. There was no fibrotic zone in the periphery of this lesion. In this lobe, a much older necrotic focus appeared to be the source from which the large pneumonic lesion arose through endobronchial dissemination.

The infrequency with which the early nonencapsulated necrotic lesion can be found in human tuberculous disease would seem to be due in large part to the chronicity of the disease and to an inability to obtain specimens at this particular phase of development. Nevertheless, lesions (Plate XIV, figure 42) can be demonstrated in man which are analogous to the early necrotic lesions observed in experimental animals.

A discussion of the morphologic features which have been observed in necrotic lesions after the initiation of an encircling zone of fibrosis will be limited to resected specimens. There are two reasons for imposing such a restriction. Resected specimens provide the pathologist with an opportunity to study residual disease at stages which hitherto have been unavailable, and from such a study clues may be found which would help to understand the potentialities of the necrotic lesions. Moreover, as the majority of the patients from whom the tissues have been removed had had chemotherapy for a few weeks to as long as three years prior to resection, it should be possible to form an opinion relative to the effect of the chemotherapeutic regimen upon the necrotic lesion. The specimens which have been removed either without any previous chemotherapy or with but a few days of such treatment have been used as a control for the other specimens.

The first general observation was that there was a lack of uniformity in the morphologic features of the necrotic foci. There also was a tremendous variation in the size and in the number of these lesions. In some lesions there was a peripheral cellular fibrotic tissue which invariably was infiltrated to a considerable degree with lymphocytes. This will be clearly evident in some of the illustrations in the following chapter on minimal tuberculosis. In other lesions there was an old hyaline fibrotic periphery which showed no lymphocytic infiltration. In between these two extremes there was a considerable variation in the cellularity of the fibrous tissue and in the amount of lymphocytic infiltration. Also, in these intermediate lesions, giant cells in variable numbers were present and, on occasion, epithelioid tubercles were also found. In some specimens in which there was considerable anthracosis, necrotic lesions with a light to dense accumulation of the pigment (Plate XIV, figure 43) in the inner portion of the fibrotic zone were present. It appeared probable that this accumulation of pigment was due to an invasion of dust-laden alveolar phagocytes which later had disintegrated. The

phenomenon is similar to that noted earlier in giant cells. In approximately one-fourth of the specimens, varying stages in the process of calcification were found in one or more lesions. Cholesterol crystals were found in some lesions, but this phenomenon was not observed so frequently as was anticipated. These various morphologic features were interpreted by the writer to indicate necrotic lesions of different ages. As necrotic lesions of different ages quite often were observed in the same specimen, it appeared that many necrotic lesions had long antedated the initiation of a chemotherapeutic regimen.

The dissimilarity in the behavior of the necrotic foci seemed to the writer to be the most significant feature found in the entire study. Many of the lesions showed no breaks on gentle bending. On microscopic study, lesions of this nature showed a continuity of an intact necrotic lung parenchyma (Plate XIV, figure 44) with the fibrotic periphery. In other lesions a break between the firm, rubbery necrotic center and the fibrotic periphery was found. On occasion this separation of the living from the dead tissue was sufficient to allow the fibrotic capsule to be easily drawn away from a solid rubbery central portion. Other lesions showed a small portion which could be easily removed with a swab, the remainder being tough and leathery. Some lesions were dry and others were moist. These and other macroscopic features were taken to represent differences in the behavior of the necrotic lesions which, in part, may be due to aging.

Microscopic study of the necrotic lesions often showed blue-tinged linear foci in the region of the junction of the living and dead tissue. In some lesions these focal areas were the seat of beginning calcification; in others only a large amount of nuclear "dust" was present; and in still others a heavy infiltration of easily identified neutrophils occupied the area. This was the area of the necrotic lesion in which a disintegration of the necrotic tissue had led to a separation of the dead from the living tissue.

In some lesions, material of the consistency of thick cream was found in the peripheral portions of the necrotic zone. Microscopic examination of lesions of this type sometimes showed only amorphous granular debris in these areas, whereas in other lesions the area was heavily infiltrated with neutrophils. From the variations observed it would appear that a focal disintegration of the necrotic tissue had been induced by the invasion of neutrophils which in turn had disintegrated, and the progress of liquefaction had been brought to a halt. Perhaps focal areas of this nature might occur time and again without the accomplishment of complete liquefaction of the necrotic tissue. Careful search of the peripheral portion of the necrotic tissue seldom revealed any tubercle bacilli, and this pertained as well to foci in which neutrophils were numerous. Perhaps this focal process may be induced merely by a change in the chemical processes within the necrotic tissue. Features such as calcification (Plate XV, figure 45) and formation of cholesterol crystals would seem to indicate that, chemically, a state of flux exists in the necrotic tissue.

Liquefaction of only the area of necrotic tissue in the region of a connecting bronchus could readily give rise to small sloughs and to endobronchial disseminations. This process probably accounts for the increase of shadows in roentgeno-

grams which show no evidence of cavity formation. It cannot be emphasized too strongly that liquefaction of an entire necrotic pneumonic lesion is not necessary before sloughing can take place. Failure to demonstrate tubercle bacilli in sputum under these conditions could be explained either by the small amount of the slough or by the paucity of bacilli in the sloughing debris.

Not only did the amount of liquefaction of necrotic lesions vary from specimen to specimen, but also the number of necrotic lesions which were infiltrated with neutrophils and were undergoing liquefaction varied greatly. In some specimens, only one or two necrotic lesions showed evidence of partial disintegration, and these contained no identifiable neutrophils. In other specimens the majority of the necrotic foci (Plate XV, figure 46) showed a heavy infiltration of neutrophils and, to a considerable degree, a disintegration of the necrotic lung framework. Small foci of recent lobular pneumonia were found on occasion in specimens of this type. This condition was found in specimens which had been removed from patients who had been on a chemotherapeutic regimen for as long as a year.

On occasion a specimen (Plate XV, figure 47) would show some necrotic lesions with no recognizable cellular elements and an intact dead lung framework; others were undergoing calcification; in still others there was a partial disintegration of the dead lung framework but without recognizable cellular elements; and in one or two there was a heavy infiltration with neutrophils. The latter lesions indicated that a progressive active liquefaction of the necrotic tissue was well on its way. In one specimen a lesion (Plate XVI, figure 48) with a considerable area of early calcification showed a heavy infiltration of neutrophils in adjacent areas. Large necrotic lesions (Plate XVI, figure 49) sometimes showed one portion which was heavily infiltrated with neutrophils and no evidence of disintegration of the dead tissue in the major portion of the lesion. Usually, but not necessarily, the area with neutrophilic infiltration in such lesions was in the region of the connecting bronchus. This situation was found in specimens which had been removed after a variable period of chemotherapy.

It would appear from this study of the necrotic parenchymal foci that their individual behavior is unpredictable. Lesions of similar macroscopic appearance can show a very dissimilar microscopic picture. The necrotic foci in specimens which were removed from patients who had either little or no chemotherapy closely resembled those in specimens which were removed after a considerable period of chemotherapy. It would seem that chemotherapy per se had not affected the morphologic appearance of this type of lesion. Another finding of importance was that, in some cases, chemotherapy did not prevent a continuation of the process of liquefaction. How much it may affect this process in general is not at all clear. The continuation of the process of liquefaction during chemotherapy serves to indicate that necrotic lesions, once formed, do not behave in the same manner in all tuberculous patients.

The unpredictability of the behavior of the necrotic lesion probably is intimately related to the unpredictability of the occurrence of clinical relapses of tuberculosis. On a statistical basis it can be shown that, in a large group of tu-

berculous patients, relapse occurs according to a regular predictable pattern. Perhaps the necrotic lesions in a large group of tuberculous patients may also behave with a predictable regularity. There is no means available at the present time, however, to select individual patients who certainly will suffer a relapse of the disease, and it is on an individual basis that tuberculous patients must be managed.

THE SOLITARY PARENCHYMAL LESION

This necrotic lesion has been called a solitary lesion, a coin lesion, and a tuberculoma. In the resected specimens which the writer has studied there were ten lesions of this type. Acid-fast bacilli were demonstrated in eight specimens and, in the other two, remnants of fungi were found. All but two of the lesions were resected because of the possibility of neoplasm. Although the major portion of disease consisted of a single large lesion, small independent necrotic foci were also present in each specimen. To the writer this indicated that small focal endobronchial disseminations had occurred. The size of the major lesion varied from 1 to 4 cm. in diameter.

These lesions were of a yellowish-gray color and had a firm rubbery consistency. On section, two of the lesions presented a rather regular laminated appearance. Microscopic study of these lesions showed that the major portion was made up of dead fibrotic tissue and that there was a considerable amount of old fibrin at the junction of the lamina. In an area in the central portion, however, a dead lung framework was present. In these lesions it would appear that there had occurred a succession of necroses of newly laid-down peripheral fibrotic zones and that the lesion had become enlarged through this process. Acid-fast bacilli could not be found in the region of any of the zones of lamination; however, they were found in the central area in which a framework of dead lung was seen. The reason for the lesion's development into a laminated structure was not evident.

In the remaining lesions (Plate XVI, figure 50), multiple areas of necrotic lobular pneumonia were present. In the more complex lesions, some of the areas of necrotic pneumonia apparently had been surrounded by a fibrotic zone before other lobular areas became involved, and in these lesions there was an irregular lamination. The laminations were found to be necrotic fibrous tissue about a necrotic pneumonic lesion. Even though the structure suggested that lesions of different ages were present, the lesion as a whole seemed basically to be a necrotic pneumonic process.

THE BEHAVIOR OF CAVITY

In the treatment of pulmonary tuberculosis, no feature is more difficult to control than cavity formation. Bed-rest therapy, pneumothorax, interruption of the phrenic nerve, pneumoperitoneum, thoracoplasty and, more recently, chemotherapy have all been utilized to induce closure of cavity. While all of these procedures may be of value, none has proved to be completely successful. The serious implication of demonstrable cavity is as manifest as is the necessity of

inducing a closure of this structure. Therefore, it is rather disappointing that greater attention has not been paid to the pathologic process which precedes the evident cavity that is found in chest roentgenograms.

Cavity formation indicates that an area of necrotic tuberculous pneumonia (Plate XVII, figure 51) has undergone liquefaction to a great extent and has sloughed through a connecting bronchus. Although large cavities usually indicate that a considerable area of a necrotic and liquefied tuberculous pneumonia has sloughed, the size of a cavity cannot always be regarded as a true indication of the amount of lung tissue which was originally expectorated. Unfortunately there is never a complete liquefaction of the necrotic tissue at the time of cavity formation. Liquefaction and sloughing of the remaining necrotic tissue continue after the cavity has been formed.

Study of the inner portions of tuberculous cavities shows that in some areas only healthy granulation tissue is to be found, without demonstrable tubercle bacilli. In other areas neutrophils predominate in the inflammatory cells which have infiltrated dead tissue, and in these areas tubercle bacilli may or may not be numerous. In still other areas there may be only necrotic tissue with no identifiable cellular elements. Some of these areas may show no bacilli, whereas in other areas bacilli may be present in tremendous numbers, sometimes in colony formation. This very irregular distribution of bacilli is a common feature, and it is unusual to find bacilli much beyond the innermost portion of the cavity wall. With a situation such as has been described, it seems probable that areas of healthy granulation tissue eventually may become infected and may subsequently undergo necrosis. Hence, a vicious cycle may be set up in which areas are cleansed of necrotic tissue, only later to become infected and the whole process of necrosis, liquefaction, and sloughing repeated. This, perhaps, is the basic reason for the inability of tuberculous cavities to heal.

In the study of cavity walls, little evidence was found to indicate that the infection had penetrated the wall and extended into the surrounding lung tissue. Instead, the evidence would seem to indicate that in general the fibrotic periphery is an effective barrier between the surrounding lung parenchyma and the zone in which tubercle bacilli reside. The inner portion of the peripheral fibrotic zone undoubtedly often undergoes necrosis; however, no instance was found in which the entire fibrotic zone had necrosed.

Roentgenograms frequently show cavity walls of different thicknesses. This difference in thickness is due in some instances to the amount of organizing fibrotic tissue; in other instances, the major portion of a thick cavity wall may be composed of necrotic intact lung tissue. The thickest cavity walls which the writer has studied belong in the latter category.

An initial clinical diagnosis of advanced disease had been made in 240 of the 295 patients from whom tuberculous disease had been resected. Evidence of one or more cavity formations was found in 188 of the specimens removed from these patients. In 47 instances open cavities were present. In the remaining 141 cases the cavities were either closed or filled-in, or were represented by a stellate scar. The criteria used in designating a filled-in cavity were: the presence of

necrotic contents which were soft and pultaceous, could easily be removed with a swab, and gave no evidence of lung structure on microscopic examination.

One hundred and thirty-eight of the cavities were filled-in and, in ninety-eight, a patent bronchial communication with the necrotic zone was demonstrated, either by a flexible thin wire probe or on microscopic examination. In only one instance was a complete fibrotic closure of the connecting bronchus demonstrated. In this specimen serial sections showed that the bronchus was completely closed by scar tissue. In three specimens a stellate scar was found which was interpreted, on macroscopic evidence, to represent a cavity which had completely healed by scar formation. Microscopic study of different levels gave no evidence of necrotic remnants in two of these scars. In the third specimen, however, the small necrotic remnants (Plate XVII, figure 52) of the cavity were found, and this area was in direct communication with a bronchus. It appears that closure of cavity, as seen in roentgenograms, indicates that the shrunken remnants usually remain as a necrotic lesion which commonly has a patent communicating bronchus. Sealing off of a filled-in cavity by obliteration of its connecting bronchus is not a common occurrence. Complete healing of a cavity by scar formation is unusual.

It would appear from the study of necrotic lesions which had not yet sloughed that liquefaction of dead lung tissue was a prerequisite for cavity formation. It is possible that a tuberculous abscess can undergo liquefaction and slough prior to a complete necrosis of the lesion. On occasion one finds at necropsy cavities (Plate XVII, figure 53) with walls which show little, if any, fibrous tissue. These probably represent a sloughing of a necrosing pneumonic lesion before sufficient time had elapsed to permit the formation of a fibrotic wall. A similar condition was found, on occasion, in a large tuberculous pneumonic lesion. Sometimes even the pleura became necrotic and liquefied so that a pleural fistula (Plate XVII, figure 54) was produced. Lesions of this nature do not show, in roentgenograms, the more or less spherical high light which commonly is associated with cavity formation.

The irregular areas of liquefaction found in large pneumonic tuberculous lesions usually have been attributed to the presence of a mixed infection, for bacteria other than tubercle bacilli frequently can be grown from such tissue. To the writer it is highly probable that this process may be related solely to the tuberculous infection. This is probably the process which prevails in acute "galloping" consumption. Evidently it is not the common process of cavity formation.

If one may judge from the evidence found in the study of resected specimens, the usual process in cavity formation is the laying down of a fibrotic zone peripheral to the necrotic lesion before liquefaction and sloughing occur. The lapse of time between the formation of the fibrotic zone and the slough of the necrotic debris would appear to vary greatly.

In one case in the writer's material a solid lesion had been observed in roentgenograms for four years before a "doughnut" cavity made its appearance. In another case (Plate XVIII, figure 55) more than two years elapsed before a crescent-shaped cavity was observed in the area which had been occupied by a

solid dense lesion. In one specimen, a sloughing old necrotic lesion was found in the midst of several other old nonsloughing necrotic foci. From these remarks it would seem that cavity formation depends in large measure on the tendency of necrotic areas of tuberculous pneumonia to liquefy and slough.

BEHAVIOR OF CAVITY UNDER PNEUMOTHORAX AND UNDER THORACOPLASTY

Among the resected specimens, twenty-five had been removed one to fifteen years after thoracoplasty and twelve had been removed after eighteen months to four years of pneumothorax. Pneumothorax had been in use in one case for seventeen years prior to thoracoplasty. The right upper lobe was removed twenty years after the first induction of pneumothorax. In this specimen, examination of the markedly shrunken lobe showed a filled-in cavity (Plate XVIII, figure 56) which occupied the major portion of the posterior segment. The bronchi to the posterior and apical segments were markedly distended with mucopurulent secretions and showed considerable necrotic endobronchial tuberculosis beyond a markedly stenotic bronchus. How long the stenosis of the bronchi had been in process was not known, but a small necrotic open area which was too small to be seen macroscopically was still present. This patient had continued to have sputum which was occasionally positive for tubercle bacilli on microscopy or culture during the entire twenty-year period. Acid-fast bacilli were fairly numerous and were irregularly distributed in the filled-in cavity. There were numerous necrotic lesions in the anterior segment, most of which were densely calcified. In some of the calcified lesions there was a bony metaplasia.

In a second case, pneumothorax was instituted ten years prior to thoracoplasty, and for several years the pleural cavity had been filled with oil. In this markedly shrunken lung there were many large necrotic lesions, none of which showed any calcification, and a 1 cm. cavity was present in the superior segment of the lower lobe.

In two instances the major disease was found to be related to bronchiectasis. This subject will be discussed in a later chapter.

In the remaining thoracoplasty cases, either slitlike or filled-in cavities in which some degree of sloughing was going on were found. Bronchial connection with cavity was found in all instances either by probe or on microscopic study. In five specimens, some areas of the cavity wall (Plate XVIII, figure 57) were covered by stratified squamous epithelium. Although these patients had chemotherapy, the duration of cavity and of thoracoplasty prior to chemotherapy had been so long that it was doubtful that the partial epithelization was related in any way to chemotherapy. There was a thick zone of fibrosis in the cavity wall in some instances and, in others, the cavity wall was thin.

In most of the specimens there were additional necrotic lesions which varied considerably in number and in size. In a few of the specimens, epithelioid tubercles without evidence of fibrosis, small necrosing lesions, and small foci of recent lobular pneumonia were seen, indicating that endobronchial dissemination of recent origin had occurred. A marked amount of parenchymal scarring was

present in some of the specimens, whereas in others there was little evidence of this process.

In one case, thoracoplasty was performed fifteen years prior to resection of the lung. The patient was then well clinically for ten years, at which time pulmonary hemorrhages occurred and the sputum showed acid-fast bacilli on microscopy. Hospitalization with a modified bed-rest regimen was advised, and combined chemotherapy was instituted eighteen months prior to resection of the lung. The sputum continued to contain tubercle bacilli.

The resected lung showed many small necrotic lesions with dense calcification of most of them. The presence of three cavities was established. In one, the necrotic contents were densely calcified; in a second, the necrotic contents were not calcified and were, in focal areas, invaded by neutrophils; and the third cavity was open. This open cavity showed little evidence of healing. To the writer, the difference in behavior of these three cavities under an excellent thoracoplasty, in so far as collapse of the lung was concerned, is most puzzling. This case serves well to emphasize the unpredictable behavior of necrotic parenchymal tuberculosis.

From the study of these specimens, it is evident that tuberculous cavities remain either as slitlike affairs or in a filled-in state indefinitely under thoracoplasty. In none of the specimens was the original site of the cavity represented by a scar. Search for a patent bronchial communication was made in all but two of the specimens, and in each instance a bronchial connection was demonstrated either by probe or on microscopic examination.

All of the pneumothorax specimens were removed at the time decortication of the lung was done. In five instances, only a portion of a lobe was removed; in five instances a lobe was resected because the extrapleural fibrosis could not be removed; and in two instances a lobe was resected because it contained an open cavity.

The lobes with open cavities (Plate XIX, figure 58) were largely airless and showed only a few small necrotic foci and some small scars. The cavities contained little exudate; the structure of the cavity wall was not unusual; and no evidence of epithelization was seen. The bronchi leading to the cavities showed no evidence of ulceration; however, there was a considerable lymphocytic infiltration of the mucosa. Except for the tortuosity of the communicating bronchi, there was no apparent reason for failure of the cavities to close. Perhaps there may not have been enough sloughing to permit a plugging of the bronchi and thus prevent a passage of air.

In all of the remaining specimens, at least one filled-in cavity was found (Plate XIX, figure 59), each of which had patent bronchial connection. In five of the specimens, the necrotic content of the filled-in cavity was infiltrated with neutrophils. There was only slight lymphocytic infiltration of the cavity walls in most of the specimens. In some of the specimens necrotic foci other than cavitary lesions were fairly numerous. The necrotic foci were small in size and few in number in two specimens. There was remarkably little parenchymal scarring in some of the specimens, and in no instance were lesions of recent origin seen. No evidence of necrotic endobronchial disease was found.

Although only a few specimens were studied, it would appear that tuberculous disease under pneumothorax behaves in a manner similar to that observed under thoracoplasty. Disappearance of cavity usually indicated only that these structures had shrunk and had become filled with necrotic debris. In one-half of the specimens the presence of neutrophils showed that the process of liquefaction was still in progress.

These specimens afforded an opportunity to study the fibrotic process which prevented a re-expansion of the lung. In some specimens a considerable infolding of the lung parenchyma had occurred. Usually the extrapleural fibrosis which prevented the re-expansion of the lobe did not extend into these folded areas. The extrapleural fibrosis in many areas had no connection with the pleura. However, if there were areas of parenchymal scarring which involved the pleura, a symphysis between the pleura and the extrapleural fibrous tissue was common.

In some specimens the symphysis was quite extensive, and in others it was slight. This situation would seem to determine whether the extrapleural fibrous tissue could be easily and cleanly peeled off. In these specimens it was, of course, not possible to determine the condition which initiated the fibrotic process. No evidence was found which would suggest that there had been an actual tuberculous infection of the pleural space.

THE HEALING OF OPEN CAVITIES

The writer has never seen a completely healed open tuberculous cavity. He has seen old cavities (Plate XX, figure 60) in which only a slight lymphocytic infiltration of the dense fibrotic wall was present and in which, in considerable areas, there was no necrosis of the inner surface of the fibrotic tissues. These can be considered as areas in which a clean slough has occurred and over which a growth of epithelium has not occurred. In such cavities, however, areas with a necrotic inner surface in which it was possible to demonstrate bacilli were also present and, in such areas, there sometimes were no identifiable cellular elements. Other old cavities (Plate XX, figure 61) have been observed in which the inner surface was covered to a varied extent with stratified squamous epithelium. However, in these same cavities other areas were found in which there was an active necrotizing and sloughing process. Situations such as these have been observed only in necropsies on patients who have had a long clinical history of tuberculosis. These observations were made before the era of chemotherapy, and it must be confessed that in that period the writer did not make so thorough an investigation as has been the practice with resected specimens. These remarks are made merely to indicate that, before the era of antimicrobial therapy, evidence of partial healing of cavities had been observed.

In the study of the resected specimens, evidence of some epithelial covering of the inner surface of a cavity has been observed more often than previously. The writer is of the opinion that these findings probably are due to the thoroughness with which the specimens have been studied. Extensive growth of epithelium over the inner surface of a resected cavity has not been observed. Areas of cavity walls have been found in which there was no necrotic tissue, but in these

same cavities there were other areas in which an active necrotizing and sloughing process was present. In three instances, the roentgenographic evidence of cavity was confounded by the presence of cystic bronchiectasis. In some areas the cystic bronchi had no epithelial lining, and this fact could lead to an erroneous impression that the bronchial wall represented the wall of a tuberculous cavity. This situation will be considered in greater detail in the chapter on tuberculosis and bronchiectasis.

GENERAL COMMENT

The writer has felt obliged to enter into considerable detail in the discussion of the parenchymal lesion because many controversial points had to be covered. An attempt has been made to steer a guided course through the complex morphologic features which are representative of the different ways in which parenchymal lesions behave. The presentation may appear to be repetitious. If so, it is because the morphologic features of parenchymal lesions are repetitious. The lesions under consideration are a sequel to the liquefaction and sloughing of a minute initial pneumonic focus. In brief, one may state that parenchymal disease is composed of a favorable and an unfavorable component.

The favorable component consists of the lobular pneumonia which either heals completely by resolution or proceeds to the formation of epithelioid tubercles which in time heal by scar formation. The lobular pneumonia would seem to be largely, in many instances, an inflammatory response to the dispersed necrotic tissue. Tubercle formation would seem to be the reaction to the presence of a few tubercle bacilli, although the possibility must be entertained that this lesion on occasion might also be a response to necrotic tissue.

The unfavorable component is the pneumonic focus which undergoes necrosis. Liquefaction, induced apparently by reinvasion of neutrophils, and sloughing of the necrotic debris through a connecting bronchus lead to cavitation of either microscopic or macroscopic proportions. The slough may be dispersed into hitherto uninvolved lung parenchyma, and the whole train of events is then repeated. A favorable disposal of the cavity formation is unusual because of a repetitious process of necrosis, liquefaction, and slough. A long-delayed liquefaction and sloughing of a necrotic lesion may occur, and it is the unpredictable behavior of lesions of this nature which constitutes the hazard of relapse of disease after a clinical state of health has been gained. The process of necrosis in itself appears to be essential for the destruction of tubercle bacilli in large numbers. Unfortunately all bacilli may not be destroyed in the process and the survivors apparently are able to reproduce, sometimes to tremendous numbers, in the necrotic tissue.

Any appraisal of the effect of chemotherapy on the disease process, which is based on resected specimens, must be tempered by a recognition that the resected disease was present to a considerable degree prior to the institution of treatment. The morphologic features of the necrotic lesions indicate that in many instances such lesions had been present for a long time. The infrequency with which the non-necrotic component was found in persons who had received

chemotherapy for four months or longer indicates a favorable effect of the drugs. Also, it is possible that the process of liquefaction and sloughing may have been considerably slowed down. The reason for this is not apparent. That it has not been stopped is evidenced by the presence of neutrophils, often in large numbers, in the necrotic debris contained in cavities which have remained open (Plate XX, figure 62), in cavities which have filled in, and in necrotic lesions which have not yet become liquefied. Moreover, in several specimens small, recent foci of lobular pneumonia were found. Evidence of a continuing process of liquefaction was found in specimens which had been removed more than two years after the institution of therapy.

The general morphology of necrotic lesions does not appear to be altered by the use of chemotherapy. There was a considerable variation in the manner in which the disease behaved in different patients. Similar variations were present in tissues resected from patients who had received either pneumothorax or thoracoplasty and little or no chemotherapy. To the writer, the continuation of the process of liquefaction represents the greatest hazard of residual necrotic disease, and this phenomenon is not always evident prior to a microscopic study of the specimens. The subtlety with which liquefaction occurs renders questionable any decision as to the length of time chemotherapy should be used. Tubercle bacilli, no matter how numerous, can hardly be of great import so long as they remain incarcerated in the necrotic lesion.

One feature which needs consideration is that, on occasion, dispersed necrotic debris and minute foci of early lobular pneumonia have been observed microscopically in areas in which macroscopically no lesions were suspected. Lesions of this nature are not sufficiently firm to be recognized on palpation and they would be unsuspected at the time of surgery. They do not have the firmness of either well-formed histologic tubercles or minute necrotic lesions. However, such foci appear to be the type which respond best to an effective chemotherapeutic regimen, and the possibility of their presence needs recognition in the Post-surgical management of patients.

PLATES XIII–XX

PLATE XIII

FIG. 37. (× 15) The major number of alveoli are filled with necrotic debris and there is no evidence of inflammatory cellular reaction. This suggests that the dispersion of this debris occurred either shortly before or during the operation. In the right center is a small area of recent lobular pneumonia, and it is probable that this represents a reaction to dispersed necrotic debris. A lesion of this nature need be no more than a week old. To the left of this lesion is a sizable blood vessel filled with blood.

This section serves to illustrate a probable common beginning of parenchymal lesions induced by endobronchial dissemination. This patient had been on multiple-drug therapy for eight months and had shown no evidence of increase of disease at any time. The writer has seen several lesions of this kind, and they serve to show that small endobronchial disseminations do occur during chemotherapy. Situations of this nature indicate the necessity of continuing chemotherapy for several months after surgery in order that these small lesions may become completely healed.

FIG. 38. (× 4) White male, age thirty-six. Case discussed in text. The area of disease illustrated had shown stationary roentgenographic shadows for three years prior to death. The numerous small lesions are "epithelioid" tubercles, most of which show a considerable amount of fibrosis. The bluish tinge of the necrotic lesions is due to considerable amounts of nuclear "dust" and, in a few areas near the periphery, neutrophils were identifiable. The larger lesion shows partial breakdown of the necrotic lung parenchyma, and in the smaller one this framework is intact. The patient had had no chemotherapy and died from causes other than tuberculosis.

FIG. 39. (× 15) White female, age thirty-one. Discussed in text. The predominant feature of this illustration is the presence of large numbers of "epithelioid" tubercles. In the central portion these lesions have healed by scar formation, and in the lower portion there is little fibrotic organization. There were several necrotic lesions similar to the one illustrated. It seems probable that some of these necrotic foci had been "leaking" and local endobronchial disseminations had occurred, although by roentgenography the lesion had been stationary for five years.

FIG. 40. (× 5) The predominant lesions in this illustration are parenchymal scars which are regarded as healed non-necrotic pneumonic lesions. The numerous small blue foci are collections of lymphocytes. The lesions at the top represent the remnants of a cavity. The necrotic remnants are infiltrated considerably with neutrophils, thus indicating that the process of liquefaction is at work. The patient had been on multiple-drug therapy for six months.

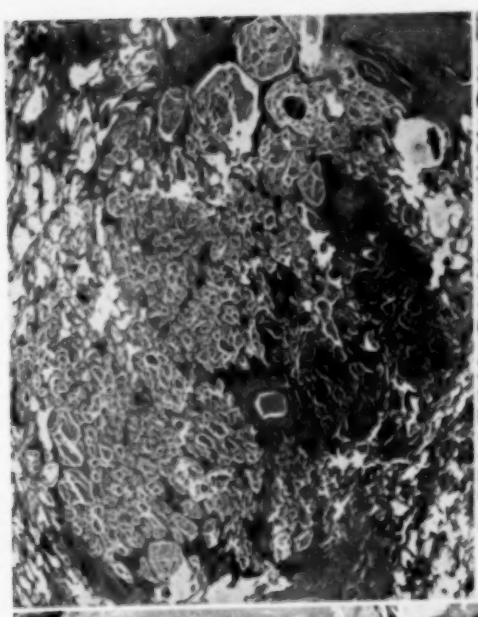


Fig. 37

Fig. 38

Fig. 39

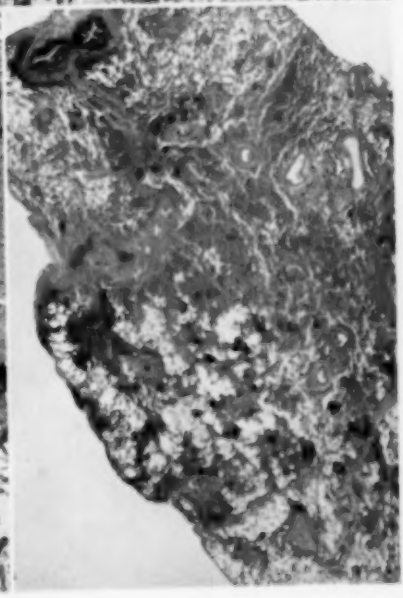


Fig. 40

PLATE XIII

PLATE XIV

FIG. 41. (× 4) Section shows extensive parenchymal scarring, a number of small necrotic lesions, and considerable obstructive emphysema with bullae formations in the left half. In the scarred area, considerable anthracotic pigment and small collections of lymphocytes are present. The latter are the blue spots. The patient was first treated for tuberculosis ten years previously. His disease relapsed one year before surgery; he was on multiple-drug therapy for ten months prior to operation.

FIG. 42. (× 15) This lesion shows the early stage of necrosis, prior to any fibrotic encapsulation, of a tuberculous lesion which would either liquefy and slough promptly or undergo complete necrosis with a possibility of later liquefaction and sloughing. Note the thin red periphery. This is the area in which necrosis is first demonstrable in experimentally produced lesions which later become completely necrotic. Lesions in this phase are most difficult to obtain from man for study, probably because the process of necrosis proceeds rapidly once it has begun. It is completed in a matter of a week or ten days in a primary infection in animals and even more rapidly in reinfection. The blue color of the area within the necrotic rim is due to heavy infiltration with neutrophils. The lung framework is intact. A blood vessel is involved in the upper portion. This lesion was obtained at necropsy on a patient who died ten days after pulmonary hemorrhages started. The lesion probably is not more than one week old. The patient had been on multiple-drug therapy for eighteen months, with sputum negative for tubercle bacilli for sixteen months. Relapse of disease occurred five months after chemotherapy was stopped, with reappearance of tubercle bacilli in the sputum. Tests showed that the strain of bacilli obtained was completely susceptible to both streptomycin and PAS.

FIG. 43. (× 15) The small necrotic lesion and the edge of an old large necrotic lesion in the lower part of the illustration show a considerable accumulation of anthracotic pigment in the inner portion of the fibrotic "capsule." In lungs in which there is a rather large amount of pigment, these old necrotic foci show this striking picture. In the opinion of the writer, this accumulation of pigment is best explained by dust-laden "alveolar" phagocytes (monocytes to the writer) which have wandered into the area, have disintegrated, and have left behind the contained pigment. To account for the large accumulation of pigment shown in the illustration would require the migration of large numbers of dust-laden phagocytes and the passage of considerable time. This illustration serves to indicate that changes are occurring constantly, although slowly. Necrotic lesions should be regarded as dynamic rather than static in character.

FIG. 44. (× 15) This is a portion of the central part of a necrotic lesion which measure 1.3 cm. across. In the lower left-hand quadrant there is an elongated piece of dead cartilage. This identifies the bronchus which lay below and is largely filled with granular debris. In the center, 2.5 cm. above the lower edge of the picture, there is a dead blood vessel full of dead blood. In the remainder of the tissue, the intact dead alveolar wall network is evident. Before cavity formation is possible, the dead lung framework has to be disintegrated through liquefaction.

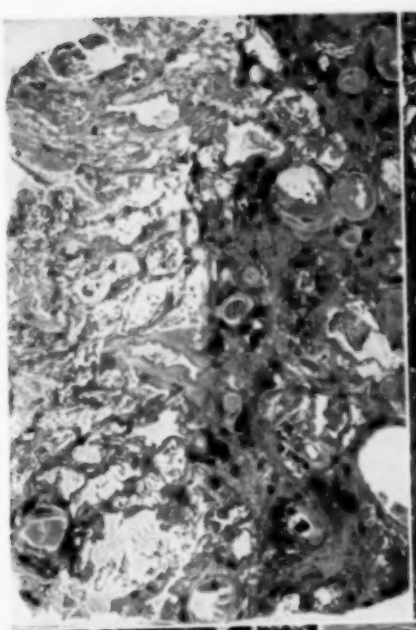


Fig. 41

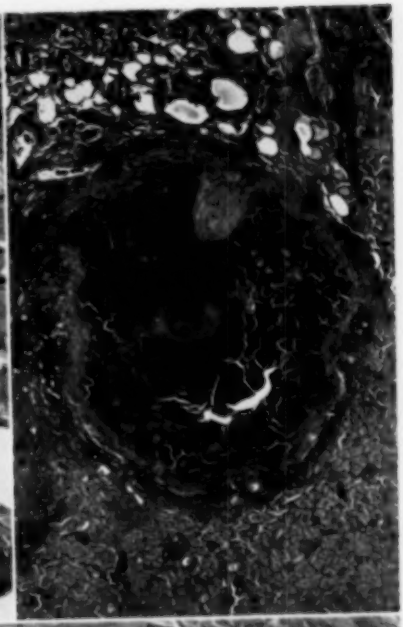


Fig. 42

Fig. 43

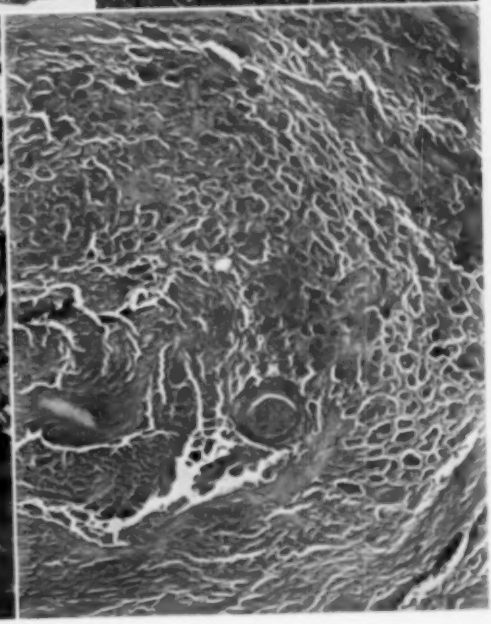


Fig. 44

PLATE XIV

PLATE XV

FIG. 45. (× 5) This is a striking illustration of an early stage of calcification found in a specimen of residual minimal disease resected after six months of chemotherapy. Grossly, there was no evidence of calcification. This was a most unusual finding in the study of resected specimens. It would seem that, if electrolytes of the blood can enter necrotic foci to such an extent, it should also be possible for chemotherapeutic agents to do likewise, provided, of course, proper chemotactic stimuli are present.

FIG. 46. (× 15) All of the necrotic lesions in the residual minimal tuberculosis resected after six months of multiple-drug therapy showed an active liquefying process at work. Below the two liquefying necrotic lesions is an area of open lobular pneumonia of recent origin. The writer has found this condition on several occasions in resected specimens. It has been found in specimens removed after more than a year of chemotherapy. In the case illustrated, chemotherapy had been in effect for seven months. Small endobronchial disseminations like this would not be seen in roentgenograms.

FIG. 47. (× 15) The group of small necrotic lesions in the left upper quadrant show early calcification which was not appreciated prior to staining the tissue. The large necrotic lesion is undergoing liquefaction and sloughing. The recent pneumonic focus to the right of the liquefying lesion is the result of endobronchial dissemination. All of the blue color in the necrotic lesion represents masses of neutrophils. Note the separation between the living peripheral fibrotic tissue and the necrotic tissue in the lower part of the lesion. Note also the fibrotic capsule peripheral to the large blue mass of neutrophils. This patient was on multiple-drug therapy for seven months prior to surgery.

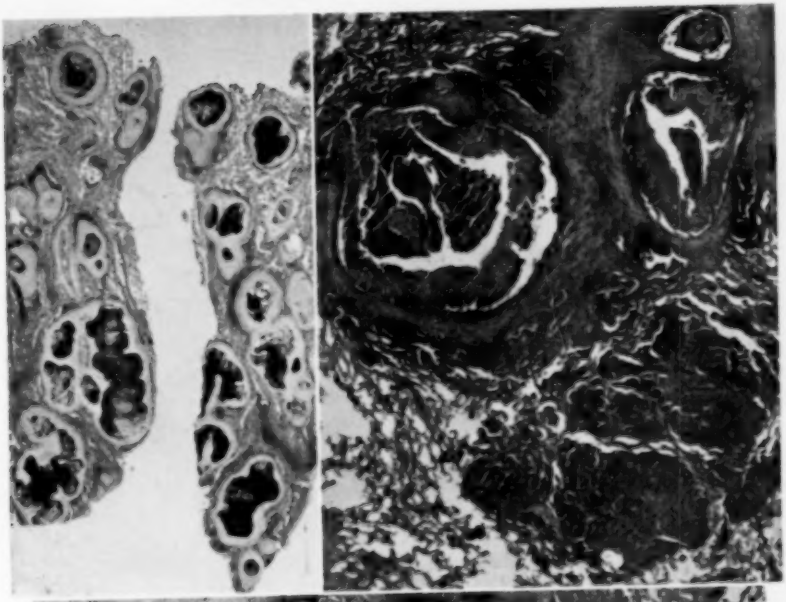


FIG. 45

FIG. 46

FIG. 47

PLATE XV

PLATE XVI

FIG. 48. (× 15) The purplish color in the necrotic area is due to an early deposition of calcium salts which was not appreciated prior to staining of the tissue. The blue color inside the fibrotic "capsule" on the left side of the lesion indicates dense accumulations of neutrophils. Note the bronchus below the necrotic focus which is filled with purulent exudate. This lesion shows calcification and liquefaction occurring in the same lesion.

FIG. 49. (× 5) In the midst of the group of necrotic lesions, there is a bronchial connection to the right of center, 1 cm. from the edge of the illustration, and in this region active liquefaction is in process. The blue color in direct connection with the necrotic areas is due to considerable infiltration with neutrophils. Some of the necrotic lesions show no evidence of liquefaction at this time. The blue spots in the extreme periphery of the necrotic lesions are due to collections of lymphocytes.

FIG. 50. (× 4) This "solitary" lesion was observed in a chest roentgenogram three years previous to resection. The roentgenographic shadow had remained unchanged. Only one of many cultures of gastric contents yielded a growth of tubercle bacilli. This occurred shortly before resection. In large part the lung framework was intact in the necrotic lesion. At one level an open bronchial communication was found. At the level of illustration the lesion is completely encapsulated, and on the left-hand side is a separation between the living and dead tissue. There is some liquefaction of the necrotic tissue in this region. Also there is considerable neutrophilic infiltration of the necrotic tissue in this area. The incision into the specimen goes through the upper edge of the bronchus which was traced into the large necrotic focus. There is some mucopurulent exudate in the lumen, and in the mucosa lymphocytic infiltration and a few tubercles may be seen. Note the several small endobronchial disseminations in the lower left-hand quadrant. Streptomycin was given only to cover the operative period.

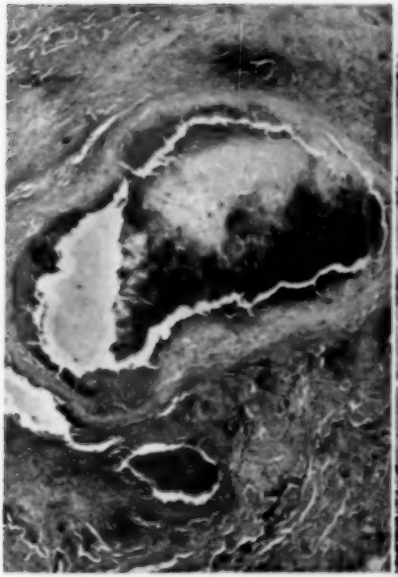


FIG. 48

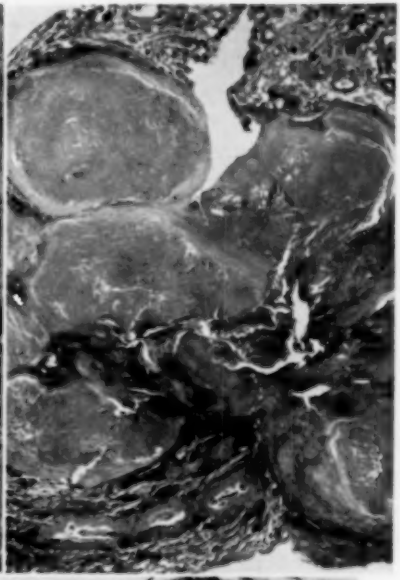


FIG. 49

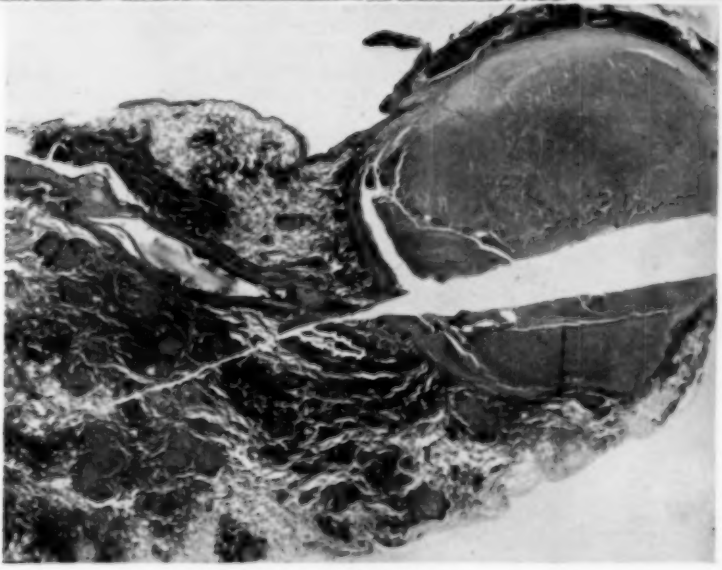


FIG. 50

PLATE XVI

PLATE XVII

FIG. 51. (× 2) Negro woman, age twenty-five; death from violence. No clinical diagnosis of tuberculosis had been made. Disease was largely limited to the posterior segment of the right upper lobe. This may be regarded as the "acute" type of tuberculosis. Evidently the necrotic foci promptly underwent softening and sloughing, and numerous small endobronchial disseminations have occurred. There is little fibrotic tissue about the sloughing lesions. In the majority of lesions the predominant cellular component is the neutrophil. Very few "epithelioid" tubercles or giant cells are present. It seems probable that this disease may well be no more than a few months old.

FIG. 52. (× 10) This shows the remnants of a cavity which macroscopically appeared to be completely healed by scar formation. The blue foci in the large scar are collections of lymphocytes. The necrotic remnants of the cavity (central portion of picture) are moderately infiltrated with neutrophils. The bronchial connection is the baylike downward projection to the left. Higher magnification would show a small area covered with stratified squamous epithelium to the left. Otherwise the bronchial structure is normal except for some lymphocytic infiltration of the mucosa. This case shows how care must be exercised in the interpretation of completely healed cavities, for the situation was not recognized prior to microscopic study. Actually this unhealed portion was only 2 mm. across, but the mechanical set-up is favorable for the tubercle bacillus.

FIG. 53. (× 2) White male, age forty-four, who died from far advanced pulmonary tuberculosis. The tuberculous cavity was present at the apex of the left lung and probably represents a sloughed endobronchial dissemination, as the major disease and cavity formation were in the right upper lobe. There is only a slight amount of fibrosis about the cavity. Evidently a considerable area of tuberculous pneumonia liquefied and sloughed before a good fibrotic zone could be laid down about the lesion. The bronchus leading into the cavity shows only a moderate amount of lymphocytic infiltration in the mucosa.

FIG. 54. (× 2) Negro male, age twenty-eight, death from tuberculosis. Extensive pneumonic lesions. Illustration shows a pleural fistula. The blue areas are due to a heavy infiltration of neutrophils. There is an acute fibrinopurulent pleuritis. Note the fragments of dead lung tissue in the area below the fistula. The majority of these lay free in the moth-eaten area of lung.

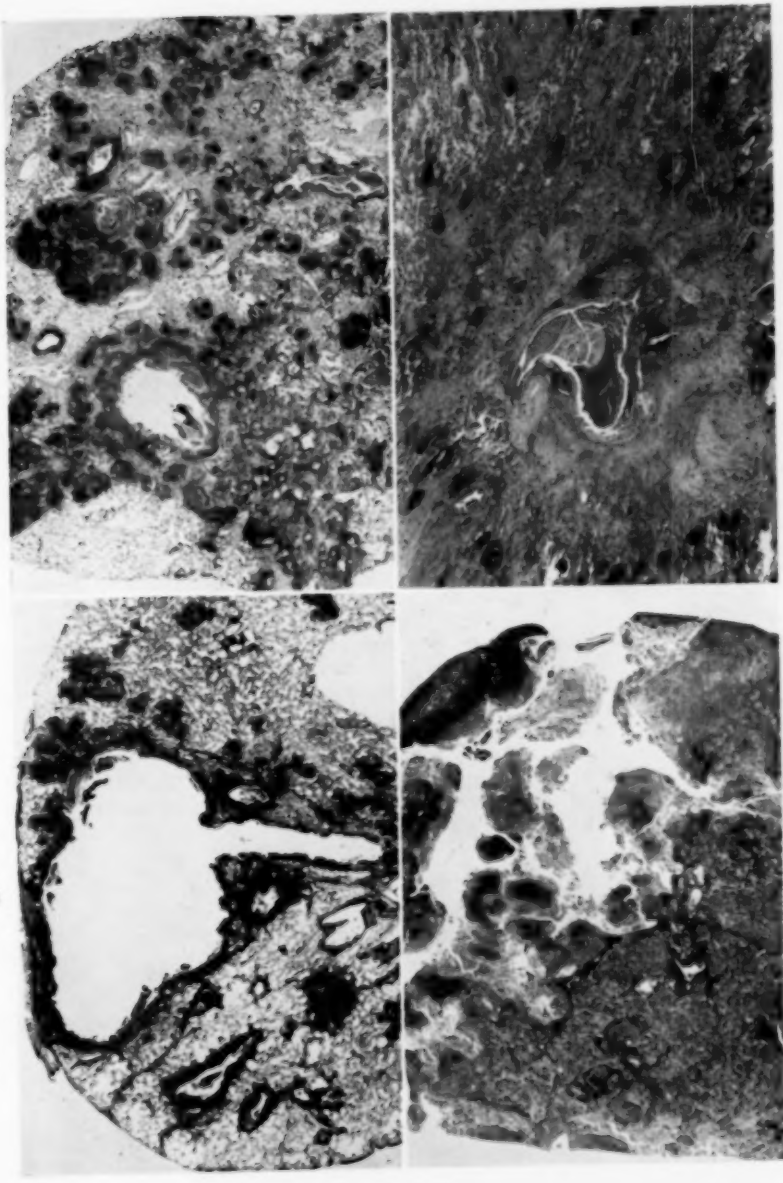


Fig. 51

Fig. 52

Fig. 53

Fig. 54

PLATE XVII

PLATE XVIII

FIG. 55. (× 4) Section from the "solid" lesion, mentioned in text, which after two years of observation revealed a crescent-shaped cavity by roentgenography; at this time there was considerable increase in roentgenographic shadows in the lobe. A well-formed, although thin, fibrotic zone surrounds the necrotic lesion. Dead lung structure was present in the nonliquefied necrotic tissue. The bluish areas inside the fibrotic capsule are areas which are infiltrated with neutrophils. The blue dots outside the lesion are collections of lymphocytes. To a considerable degree the thick "wall" of the crescent-shaped cavity was composed of necrotic lung tissue. This lesion represents a delayed liquefaction and sloughing of a necrotic pneumonic lesion. The approximate age of the lesion is not known. All that is known clinically is that the lesion did not change roentgenographically for two years.

FIG. 56. (× 4) White male, age thirty-one. Section from resected lobe of a patient who had had pneumothorax for seventeen years and then thoracoplasty for three years. Section through posterior portion of lobe from apex to base. The filled-in cavity occupied almost all of the posterior segment. Its contents were mucopurulent with bits of necrotic debris intermixed. The bluish areas are those in which an abundance of neutrophils are present. In the right upper quadrant the cystic spaces are portions of the apical segment bronchial system which was markedly distended with clear mucus. At the origin of the apical and posterior segmental bronchi, there was marked bronchial stenosis with an open sinus of microscopic proportions.

FIG. 57. (× 10) A slitlike open cavity in a right upper lobe which was resected five years after a thoracoplasty was performed. For the most part there is a thin necrotic zone which occupies the inner surface of the cavity. Bronchial connection is at the V-shaped lower portion of the cavity wall. At the apex of the V is a ciliated columnar epithelium, whereas the sides are covered with stratified squamous epithelium. This patient never received any chemotherapy.

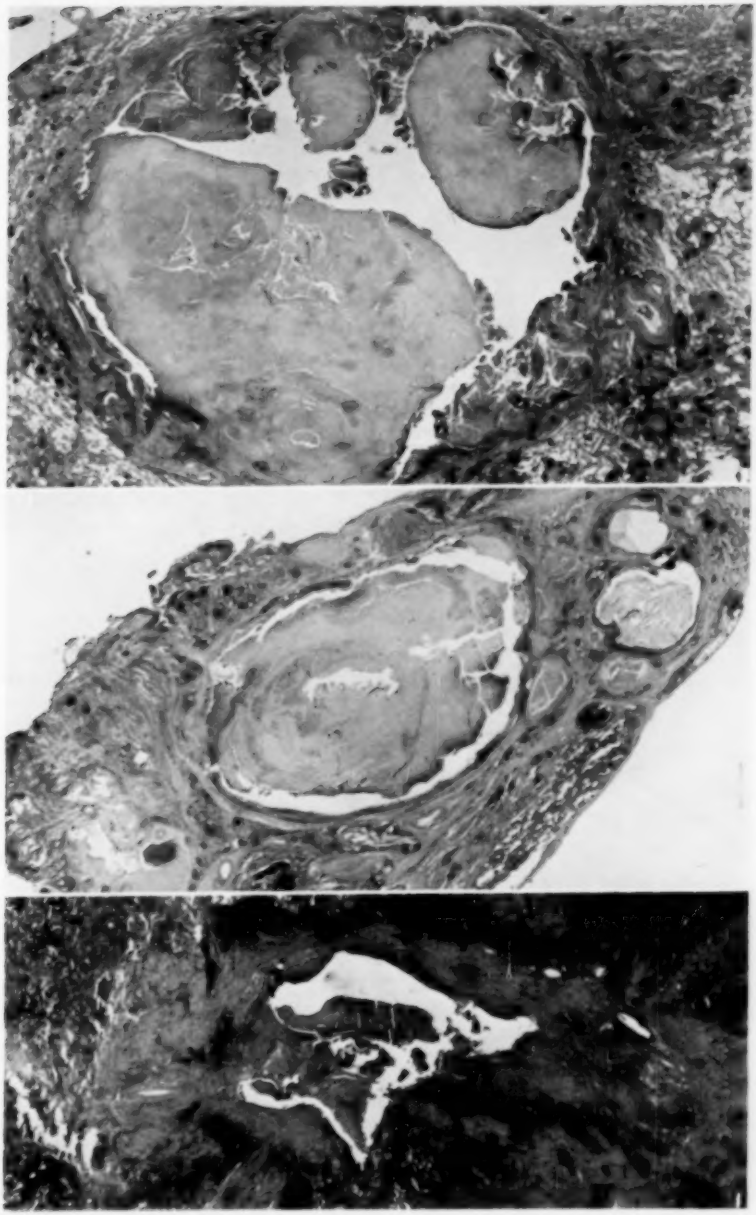


FIG. 55

FIG. 56

FIG. 57

PLATE XVIII

PLATE XIX

FIG. 58. (× 2) Open cavity in resected lobe which had been collapsed by pneumothorax for two years. Attempts to abandon pneumothorax showed that the lobe would not re-expand. Note the extrapleural fibrosis around the upper border which had "captured" the lung, although there had been no complications such as a pleural effusion. The bluish color in the inner portion of the cavity wall is due to marked neutrophilic infiltration. There is only a thin encircling fibrotic zone. The bronchus to the cavity was fully patent and showed no evidence of necrosis of the wall. It was lined with normal epithelium, and the mucosa was considerably thickened due to marked lymphocytic infiltration, edema, and congestion. This narrowed the lumen. The course of the bronchus also was tortuous. These are the only findings which might explain the reason for failure of the cavity to collapse completely. In the remainder of the lobe there were only a few small necrotic foci and a slight amount of parenchymal scarring. There had been no chemotherapy.

FIG. 59. (× 2) Section of another "captured" lobe which had been under pneumothorax four years prior to resection. Decortication of the extrapleural "peel" was stopped after it was found that the lobe was not expandable. The extrapleural fibrotic layer is present along the bottom but had been surgically removed over the upper portion. A large filled-in cavity is present at the right. At the left-hand side of the filled-in cavity are two slitlike projections to the left. The lower one of these is a bronchus which has a normal epithelial lining and a marked lymphocytic infiltration of the mucosa. There is a thin red line of blood just to the right of this bronchus. The upper slit may also be a bronchial opening but, if so, it could not be definitely identified as such. The bluish color within the necrotic zone again is due largely to infiltration of neutrophils. In this case there were many more scattered necrotic lesions as well as organizing and also healed non-necrotic foci of lobular tuberculous pneumonia. No chemotherapy had been used.

FIG. 58

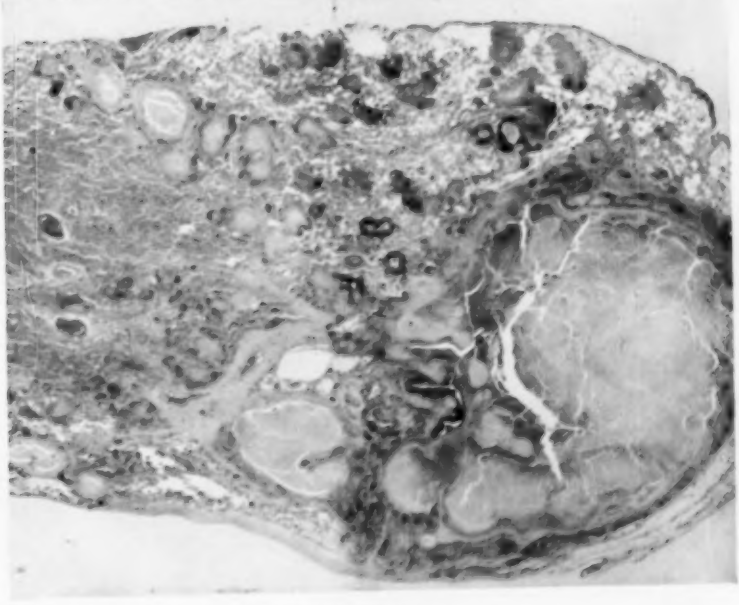


FIG. 59

PLATE XIX

PLATE XX

FIG. 60. (× 2) White male, age fifty-two. Died from peritonitis after resection of carcinoma of colon. The patient was discharged from a tuberculosis hospital as an arrested case five years previously. He had had a two-year course of bed-rest therapy; no other treatment. The tuberculous cavity found at necropsy was in the apex, and in this region the lung was firmly bound to the chest wall by old adhesions. The cavity contained little exudate, but the inner surface was composed of a thin zone of necrotic tissue. Clinically, this might be considered as a "burned-out" cavity but, pathologically, it is an open and unhealed cavity. In the surrounding lung tissue may be seen a few necrotic lesions, none of which were calcified; considerable parenchymal scarring; and areas of obstructive emphysema.

FIG. 61. (× 15) White male, age thirty-six, with a known tuberculous cavity for six years. Cavity failed to close on bed-rest therapy. Pleural adhesions prevented use of pneumothorax. Thoracoplasty was completed six weeks prior to death from causes other than tuberculosis. No chemotherapy had been used in this case. Section through slitlike collapsed cavity. In the upper right-hand quadrant the inner surface of the cavity is covered by stratified squamous epithelium. The opposite side of the cavity wall in this area shows a clean granulation tissue which is considerably infiltrated with lymphocytes. The entire inner surface of the cavity in the left half of the picture shows a necrotic zone which in places is considerably infiltrated with neutrophils. It is evident that a complete closure of such a cavity would be impossible and that a complete healing would be most unlikely. The writer has never seen a tuberculous cavity which has been healed by a complete covering of stratified squamous epithelium; neither has he seen an open tuberculous cavity in which a clean slough of all necrotic tissue has taken place. Such an occurrence is conceivable, but has not been found up to three years of multiple-drug therapy.

FIG. 62. (× 3) Negro male, age twenty-eight. Open cavities resected after three years of continuous multiple-drug therapy. The cavity was thin-walled and contained very little exudate. The inner surface of the cavity was composed almost entirely of a thin zone of necrotic tissue which was infiltrated with neutrophils to a variable degree. At one level, not illustrated, a bronchial connection was present, and for a short distance the adjoining inner surface of the cavity was covered by stratified squamous epithelium. Material scraped from the inner surface of the cavity showed an abundance of tubercle bacilli. These organisms grew readily on culture and were pathogenic for the guinea pig. They were somewhat resistant to both streptomycin and PAS.

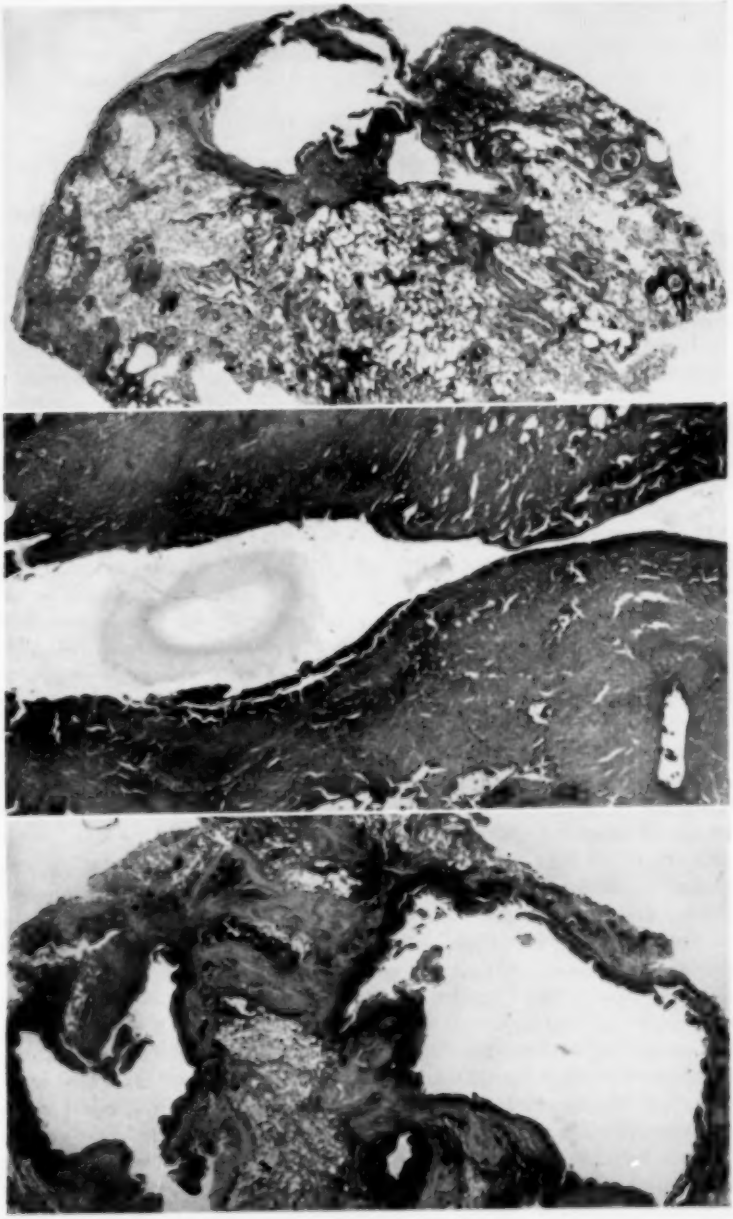


FIG. 60

FIG. 61

FIG. 62

PLATE XX

CHAPTER VI

A STUDY OF RESECTED MINIMAL TUBERCULOSIS

Great stress has been given to the finding of the early tuberculous case, and by this is meant the detection of early "minimal" pulmonary tuberculosis in roentgenograms of the chest. Perhaps new cases of "minimal" disease should be spoken of as *recently discovered* rather than *early*, for extent of disease is not synonymous with age of disease. Clinical experience has clearly shown that fewer deaths and relapses occur in patients whose disease is "minimal" in extent at the time of diagnosis than occur in patients whose disease has progressed to an advanced state. Nevertheless, before the era of chemotherapy, the most thorough studies of "minimal" tuberculosis showed that, although few died from the infection, the relapse rate ranged as high as 30 per cent. With the discovery of effective chemotherapeutic agents, a strong trend has developed to treat the "minimal" case promptly with these agents.

The experience gained from the necropsy study of cases of sudden and unexpected death convinced the writer that, clinically, early minimal tuberculosis cannot be early disease in the pathologic sense. Partial liquefaction and endobronchial sloughing of a small necrotic lesion which may be too minute to be seen roentgenographically are prerequisites for the involvement of sufficient lung parenchyma to permit detection of the lesion in a chest roentgenogram. Hence, the evidence of an "infiltrate" in a roentgenogram implies that at least one necrotic lesion is present and that tuberculous foci already are multiple.

Because of these circumstances the writer has favored, on pathologic grounds and in selected cases of pulmonary tuberculosis, surgical exploration of the chest during the period of chemotherapy and the removal of all palpable disease. As the disease frequently is a localized affair, the amount of lung tissue requiring excision often would be small. The residual necrotic lesions which the writer believes to be the source of relapses would be removed. With modern surgical technique and modern methods of anesthesiology, the hazard of the operation, although always to be regarded as a major surgical procedure, would be less than with unresected necrotic disease. The resected disease would afford an opportunity to ascertain promptly the exact status of the pathology and bacteriology without having to wait several years at least to determine the clinical course after chemotherapy. It is of the utmost importance to determine whether chemotherapy can induce a disappearance of tubercle bacilli from the lesions of minimal pulmonary tuberculosis and thus effect a complete cure of the disease.

Among the 295 tuberculous patients who underwent pulmonary resection, 40 were patients whose initial clinical diagnosis was "minimal" pulmonary tuberculosis. Only one patient was more than forty years of age, whereas 12 were between the ages of thirteen and nineteen. Twenty-three were females and

17 were males. Roentgenographic evidence of disease was found in only one lung in 36 patients, and in 4 patients bilateral lesions were noted. Bilateral resection was performed on 4 patients, so that a total of 44 lungs were examined at operation. In each case all demonstrable disease was removed. The right lung was explored in 24, the left lung in 12, and both lungs in 4 patients.

Of particular interest were the amount and the location of the resected pulmonary tissue. Fifty-five portions of lobes were removed. In nine instances the disease was scattered sufficiently to warrant removal of an entire segment. Of these, four were resections of the superior segment of a lower lobe and five of an apical, posterior, or apico-posterior segment of an upper lobe. The remaining forty-six specimens were wedges or local excisions of pulmonary tissue. Of these, six were from the superior segment of a lower lobe, thirty-eight were from an apical, posterior or apico-posterior segment of an upper lobe, and the two remaining specimens were from a basal segment and from a middle lobe. Fifty-three of a total of fifty-five specimens were from the more vulnerable portions of pulmonary lobes. In this group of patients it was evident that, although the extent of endobronchial dissemination within a pulmonary lobe varied considerably, it seldom involved more than one segment or a part of one segment.

One of the patients had received chemotherapy only a few days prior to surgery. The remaining 39 had received two months or more of streptomycin-PAS therapy prior to surgery, and in a few the chemotherapeutic regimen had been in force for eight months. The known duration of disease varied from a few weeks up to five years prior to the institution of chemotherapy.

The discussion of these cases is not concerned with a clinical evaluation of therapy; however, it is pertinent to mention that the recession of roentgenographic shadows was considerable in some cases and insignificant in others. The morphologic features found in the study of the resected lesions showed a considerable variation from case to case, and these variations can best be shown by a selection of individual cases for discussion. However, before a presentation of the cases in which the pathologic process probably was altered by the chemotherapeutic agents, it would seem advisable to present a few cases of minimal disease which had not been so treated.

The first case was that of the seventeen-year-old girl whose findings were discussed in Chapter IV, and the reader is referred to this discussion. Three other cases will be discussed briefly. They were found in the necropsy study (41) of cases of sudden and unexpected death and showed morphologic evidence of active disease. All of these were deaths from trauma. One was a twenty-five-year-old Negro woman (Plate XXI, figure 63); the second was a thirty-seven-year-old white male (Plate XXI, figure 64); and the third was a white male (Plate XXI, figure 65) in his fifties. At least one necrotic lesion which was undergoing liquefaction was found in each person. Other necrotic foci with an intact dead lung framework were also present and, in addition, there were few to many small necrotic foci and histologic tubercles with and without giant cells. An occasional small focus of early lobular pneumonia was present without evidence either of necrosis or of tubercle or giant-cell formation. In each case an occa-

sional small parenchymal scar was found. The disease found in the 3 persons can be regarded neither as of recent origin nor as of long standing since evidence of calcification was lacking and the fibrotic zone about the necrotic foci did not present the morphologic features which commonly are present in old lesions of this type. In each instance there were multiple lesions which indicated focal endobronchial disseminations.

The illustration of each case shows a section through the greatest extent of disease. The lesions were confined to the posterior segments of upper lobes. In none of the necropsy cases was "minimal" disease found of more recent origin than that present in the twenty-five-year-old Negro woman. These 4 cases show the variety of morphologic features which may be found in minimal disease. The proportions and sizes of the different components can be expected to vary considerably in different cases.

The first case of minimal pulmonary tuberculosis, the writer believes, to undergo resection after preparatory chemotherapy was a twenty-seven-year-old male medical student. At the time of enrollment in medical school, a roentgenogram of the chest showed a small shadow in the apex of the right lung. No detectable change in the roentgenographic shadow occurred during a period of ten months of conventional bed-rest therapy. Increased physical activity was then started, and after two months a new, soft, ill-defined shadow appeared which effaced the original lesion. After four months of streptomycin-PAS therapy, the new lesion had completely cleared and the original lesion seemed to be smaller than previously. Three months later a wedge resection was performed.

The piece of resected lung tissue measured 4 by 3 by 1.5 cm. There were no pleural adhesions. On palpation, four separate firm foci were felt. Three of these were between 2 and 3 mm. in diameter and the largest was 7 by 4 mm. The smaller foci were of a yellowish-gray color. The largest lesion was taken *in toto* for serial sections. Macroscopically, the remainder of the pulmonary tissue presented a normal appearance.

Microscopic examination of sections from various portions of the specimen showed the three small firm lesions to be areas of necrotic lobular tuberculous pneumonia which had a thin fibrotic periphery and an intact dead lung framework. There were some small parenchymal scars in which lymphocytic infiltration and an occasional giant cell were found. The remainder of the lung parenchyma presented a normal structure.

The writer performed the serial sectioning of the largest focus. A study of 400 serial sections showed three lesions (Plate XXII, figure 66) which, although separate in some areas, were joined together in other portions. The smallest lesion was 0.7 mm. in diameter. There was no calcification in this focus, and the lesion was an old hyaline fibrotic one. This was joined to another focus which was 2 mm. on cross-section and showed a dense calcific focus in its central portion. There was less fibrotic organization in this lesion, and a dead lung parenchyma was easily identified within the necrotic portion. This second lesion became an integral part of the largest lesion, which in greatest cross-sectional diameter measured 5 by 4 mm.

The central portion of the largest focus was composed of granular amorphous necrotic material which was infiltrated irregularly with a variable number of neutrophils. No identifiable lung structure was found in this part of the lesion. Just peripheral to this area was a thin zone of necrotic tissue which in some areas was

devoid of identifiable cells and in other areas showed a considerable infiltration of neutrophils and a few monocytes. Peripheral to the necrotic zone was an actively organizing fibrotic tissue which was heavily infiltrated with lymphocytes. In one area adjacent to this lesion was a small bronchial branch which was dilated with retained mucus. This bronchus was directly involved in the organizing scar tissue in one portion, and apparently this situation prevented a drainage of normal secretions. The bronchus was not connected directly with the necrotic lesion. An open bronchial communication with the necrotic area of the large lesion was present in four sections only. The epithelium of this bronchus was normal up to its junction with the necrotic tissue. The bronchial mucosa was heavily infiltrated with lymphocytes, and an occasional giant cell was present. A few fragments of necrotic material were found in the lumen. In the lung parenchyma around the lesion there were a few minute scars, most of which were infiltrated with lymphocytes.

A thorough search for acid-fast bacilli in sections through several different levels of the large lesion was made. A few bacilli were found in some sections and none were found in others. They were found only in the necrotic portion of the lesion. A thorough search for bacilli in several sections from other portions of the specimen failed to reveal any bacilli.

This case has been presented in considerable detail because this was the first case in the writer's series of "minimal" pulmonary tuberculosis in which a considerable course of chemotherapy had been given. The thorough study of the resected tissue showed clearly that the recent disease, which prompted the institution of chemotherapy, had either completely resolved or had healed by scar formation. It is probable that the three small necrotic foci were unrecognized minute endobronchial disseminations which had occurred at some time prior to chemotherapy. The direct association of the small old foci with the largest lesion clearly indicated the minute beginnings of the disease. This association suggests that the disease was of considerable duration, probably two or three years, at the time of its discovery. The fully patent bronchial communication with the largest necrotic focus revealed the source of endobronchial dissemination, although the lumen of this bronchus was only 80 micra, less than one-tenth of a millimeter, on cross-section.

The second case to be discussed was that of a twenty-six-year-old physician who became a reactor to tuberculin in 1948. Early in 1949 a small roentgenographic shadow was noted in the apex of the right upper lobe, and the patient was placed on a strict bed-rest regimen. There was no appreciable change in the roentgenographic shadow during the remainder of 1949. In 1950 he was placed on a regimen of streptomycin-PAS, and six months later resectional surgery was performed. No significant change in the roentgenographic findings had occurred during this period.

The resected specimen from the right upper lobe measured 4 by 2.5 by 2.5 cm., and this piece of tissue represented all of the palpable disease which the surgeons could find in the lung. The major portion of the specimen was occupied by a firm nodular mass which measured 2 by 1.7 by 1.5 cm. Except for this large lesion, the tissue gave the macroscopic appearance of normal lung. There were no pleural adhesions. A block of tissue containing the entire lesion was embedded, and a total of 1,000 serial sections with a thickness of 20 micra were obtained.

Microscopic study of the sections showed six separate lesions (Plate XXII, figure 67), each of which was surrounded by an actively organizing zone of fibrous and granulation tissue. The central portion of each lesion was composed of either necrotic debris which was irregularly infiltrated with neutrophils or purulent exudate which was composed predominantly of neutrophils. No histologic tubercles or giant cells were found. In the central areas there was little evidence of lung structure. The peripheral portion of each lesion showed slight to extensive lymphocytic infiltration at various levels. In two of the lesions there was a dense infiltration of eosinophils in some areas. In the writer's experience, this phenomenon is unusual and may perhaps be related to the chemotherapy as no similar reaction has been found in the examination of tuberculous tissue from patients who have not been given antimicrobial therapy.

In addition to the lesions just described, a rather large amount of parenchymal scarring was noted, which would suggest that non-necrotic tuberculous lesions had healed by scar formation. In the midst of one of these scarred areas a minute necrotic focus was found which was sufficiently old that cholesterol crystals were present. About this minute necrotic focus the most dense and oldest scar tissue was observed. This old focus could well represent the remnants of the initial lesion from which the remainder of the disease was propagated. No histologic tubercles or giant cells were found.

A thorough search of each of the six unhealed lesions for a direct bronchial communication, such as was found in the previous case, was unsuccessful. In the peripheral organizing tissue one or more patent bronchioles were noted which in several instances could be traced to the inner zone of marked cellular inflammation, and at this level the bronchiole no longer could be identified. In the series of sections, larger bronchial branches were present; however, these presented a normal appearance.

All of the lesions were searched for acid-fast bacilli at several levels. In the necrotic or purulent portion of each lesion a few bacilli were found, and no bacilli were observed in any other areas. Although bacilli were present, they were in small numbers and required prolonged search to discover. The paucity of bacilli was of interest in the light of the active inflammatory process.

The rather detailed presentation of these 2 cases, which had continued for approximately the same period and had had the same type of clinical management, indicates that minimal pulmonary tuberculosis is a complex rather than a simple pathologic process. In both cases the lesions were multiple and the various lesions had behaved in a different manner. In the second case the disease process was at least two years old, for the patient had become a reactor to tuberculin approximately two years before the tissue was resected. In the first case no tuberculin testing had been performed. Judging from the morphologic features found in the resected tissue, however, the infection probably was four or five years old.

In the study of the group of minimal cases, it was found that in only one instance were necrotic lesions absent. This patient was a thirteen-year-old Chinese boy from whom no tubercle bacilli had been obtained at any time and whose pulmonary shadows had undergone almost complete clearing during the course of chemotherapy. The tissue removed showed only parenchymal scars, and a

pathologic diagnosis of tuberculosis was not possible. Whether this was a case of tuberculosis cannot be stated on pathologic grounds. Certainly, the clinical course was consistent with a diagnosis of pulmonary tuberculosis. It is necessary to recognize that it may be possible for the necrotic component to be so small that it may heal completely. The residual scar of such a focus could easily escape detection unless serial sections were done. However, this situation would seem to be uncommon, at least in the 40 cases studied.

In the remaining cases necrotic foci, parenchymal scars and, in an occasional case, numerous histologic tubercles with giant cells were noted.

> This latter condition was a prominent feature in a twenty-four-year-old medical student whose chest roentgenogram in June, 1951, showed a small shadow which by June, 1952, had increased in size. Of many cultures of fasting gastric contents, only one was positive for tubercle bacilli. Early in December, 1952, a regimen of streptomycin-PAS therapy was begun, and two months later the apico-posterior segment of the left upper lobe was excised. During the two months of chemotherapy considerable clearing of roentgenographic shadows had occurred.
>
> Macroscopic examination of the specimen showed numerous small firm nodules rather widely dispersed in the peripheral portion of the segment. There were three yellowish-gray foci, each of which measured approximately 4 mm. on cross-section. All of the other lesions were of a pearly-gray color and were somewhat translucent.
>
> Microscopic examination (Plate XXII, figure 68) showed that the yellowish-gray lesions were areas of necrotic tuberculous pneumonia, whereas all of the other lesions were histologic tubercles with and without giant cells. Some of the tubercles showed a considerable amount of fibrotic organization, and a few scattered small parenchymal scars were present. Otherwise the lung tissue presented a normal appearance.

As extensive clearing of roentgenographic shadows had occurred, it would seem that to a considerable degree the non-necrotic pneumonic component had resolved. It has been unusual, in the writer's experience, to encounter a morphologic picture similar to the one found in this case, provided that streptomycin-PAS has been administered for four months or longer. This specimen affords a clue upon which to explain scattered, small parenchymal scars. It also is an excellent example to illustrate a preponderance of the non-necrotic over the necrotic component of the disease.

In contrast to the case just discussed were the findings in a nineteen-year-old female student.

> In 1948, at the age of fifteen years, the patient had been found to be a reactor to tuberculin. Yearly roentgenograms of the chest were read as normal until February, 1953, at which time evidence of disease was noted in the posterior portion of the right upper lobe. The patient was promptly admitted to a hospital and streptomycin-PAS therapy was soon instituted. Within four months extensive clearing of the roentgenographic shadows had occurred. At the outset, gastric cultures were positive for tubercle bacilli, but they promptly became negative and remained so thereafter. Late in July, five months after the institution of chemotherapy, the remnants of disease were excised.
>
> At operation the diseased area was found to be well localized. Only a portion of the posterior segment of the right upper lobe was removed, and this contained all

palpable lesions. The specimen measured 5 by 4 by 2.5 cm. Within a volume of approximately 2 cc., there were several firm nodules which ranged from 2 up to 8 mm. in diameter. The remainder of the specimen presented the macroscopic appearance of normal lung tissue. There were no pleural adhesions. On section the firm nodules were of a yellowish-gray color and appeared to be well localized. The largest nodule had a rather soft crumbly central portion, and in one area there was a 1 mm. dense calcific focus.

Microscopic examination of tissue from four different levels (Plate XXIII, figure 69), which included all of the lesions, showed several necrotic lesions and a few small parenchymal scars. There were no non-necrotic lesions or histologic tubercles. Some of the necrotic foci showed an intact dead lung framework without identifiable cellular elements within the area of necrosis, and some showed a disintegration of the lung framework with a considerable infiltration of neutrophils. In one section there was a small bronchial branch which had a necrotic mucosa, and necrotic debris was present within the lumen. This bronchus probably communicated with the largest necrotic focus.

The presence of the minute calcific focus within the largest necrotic lesion suggests a relationship which was discussed in the first resected specimen mentioned in this chapter. The calcific focus may well represent a primary tuberculous lesion which was too small to be detected in 1948 and from which a progressive minimal disease became evident in 1953. If this is a correct assumption, then it becomes evident that smoldering disease which is not apparent on the roentgenogram may considerably antedate the discovery of disease which clinically would seem to be of recent origin. In the focal dissemination of the disease, the role of the bronchus is clearly shown in this case.

The smallest amount of sharply localized necrotic disease was found in a specimen from a twenty-five-year-old housewife. The first roentgenogram of the chest that this patient had ever had was taken by a mobile X-ray unit in October, 1951. This film revealed a shadow consistent with a diagnosis of "minimal" pulmonary tuberculosis, and approximately one month later the patient was admitted to a tuberculosis hospital. One gastric culture which was positive for tubercle bacilli was obtained. The patient was placed on a modified bed-rest regimen for four months, during which time extensive clearing of the roentgenographic shadows had occurred. The patient then received streptomycin-PAS, and during the ensuing five months there was no significant change in the pulmonary lesion. Resection of the residual disease was then performed, and all palpable lesions were removed.

The resected tissue consisted of two small pieces of lung. One piece measured 1.5 by 1.4 by 0.7 cm. This tissue was firmer than normal lung, but it contained no firm nodules. Microscopic study showed numerous scarred areas in the lung parenchyma which were interpreted as healed non-necrotic tuberculous disease. The second specimen measured 1.3 by 1.3 by 1 cm. Approximately one-third of the tissue was occupied by a firm nodular lesion which measured 6 mm. in diameter. On section this lesion was of a yellowish-gray color and was found to be composed of three separate foci. The largest of these foci measured 4 mm. across, and the smallest had a diameter of approximately 1 mm. The central portion of the largest focus was soft and crumbly.

Microscopic study showed several focal parenchymal scars as well as the three necrotic lesions. The smallest necrotic focus showed extensive fibrotic organization

and contained considerable anthracotic pigment. Morphologically, this would seem to be the oldest focus. The largest lesion showed a thick actively organizing peripheral fibrotic zone and a central zone of necrotic debris which was heavily infiltrated with neutrophils. Numerous monocytes and a few scattered giant cells were present in the zone which adjoined the central area.

Study of this specimen indicated that the major component of disease was the non-necrotic element which had completely healed either by resolution or scar formation. Although the necrotic component was small, it was made up of three separate foci (Plate XXIII, figure 70) which evidently were of different ages and which had behaved in a somewhat different manner.

Serial sections were studied in the first two resected specimens presented in this chapter. One showed a definite patent bronchial communication with the major necrotic focus, and the other did not. Although a study of this nature is laborious, it seemed advisable to pursue it somewhat further. Two more specimens in which the main necrotic focus was small enough to make serial sectioning feasible were studied. One will be discussed later in some detail in the chapter on bronchial lesions in tuberculosis.

The second lesion was resected from a twenty-three-year-old white male who was a veteran of the Korean war. This man when first employed at a tuberculosis hospital was a reactor to tuberculin, and a pre-employment chest roentgenogram showed no abnormal shadows. A chest film taken six months later showed a small ill-defined shadow in the upper and posterior portion of the left upper lobe. The man was promptly hospitalized upon the assumption that here was an early "minimal" tuberculous case, and one week later a regimen of streptomycin-PAS was instituted. Several cultures of fasting gastric contents produced no growth of tubercle bacilli. After two months of chemotherapy some clearing of the roentgenographic shadow had occurred, and one month later the diseased area was resected.

All palpable disease was removed, and the piece of lung tissue resected measured 1 cm. in diameter. Within this piece of tissue, one firm lesion which was approximately 7 mm. in diameter and three much smaller separate firm foci were palpated. The entire block of tissue was serially sectioned by the writer, and 300 sections of a thickness of 30 micra were obtained.

Study of the serial sections showed one large and four separate small necrotic foci. In the surrounding lung parenchyma, a number of small scars were present which were infiltrated with lymphocytes, and a rare minute histologic tubercle was found. The remainder of the disease consisted of a necrotic lesion about which was a zone of organizing fibrous tissue which, in places, was infiltrated with lymphocytes and, in other places, contained histologic tubercles and giant cells. Within this large lesion there was a much smaller one (Plate XXIV, figure 71) which measured approximately 1 mm. in diameter and had a well-formed fibrotic periphery. The central portion of this small focus was composed of granular debris. This lesion merged with the larger necrotic center which, in part, showed an intact dead lung framework and, in part, was composed of granular debris. No recognizable cellular elements were found in the necrotic zone. In only three sections of the entire series was there a direct bronchial communication with the necrotic zone. The bronchial epithelium was normal up to its contact with the necrotic tissue, and the bronchial mucosa showed a mild degree of lymphocytic infiltration.

It was evident that a localized endobronchial dissemination had occurred in

this case. Also, it seems probable that the minute lesion which was within the confines of the larger lesion and surrounded by a fibrotic zone of its own represented the initial tuberculous focus.

One case in the group of "minimal" pulmonary disease was a white female who at the time of resection of the pulmonary disease in 1952 was thirty-five years old. From 1939 to 1941 she worked as a technician in the laboratory of a tuberculosis hospital. At this time she was a reactor to tuberculin, and roentgenograms of the chest showed a calcific focus in the right lower lobe as well as calcific foci in the lower hilar region on the right. In 1942 there was no evidence of disease in the right upper lung field. In 1946, a chest roentgenogram taken at a chest clinic showed indefinite shadows in the right upper lung field. In 1947 some increase in shadows was observed, and she became a patient in a tuberculosis hospital. She remained on a bed-rest regimen for one year, during which time fourteen cultures of fasting gastric contents were all negative for tubercle bacilli. A considerable clearing of the shadows in the right upper lung field had occurred. After discharge from the hospital, roentgenograms of the chest were made at six-month intervals in a chest clinic and in December, 1950, there was an increase in shadows in the right upper lung. Further slight increase was noted in 1951, and in August of this year a culture of fasting gastric contents gave a growth of two colonies of tubercle bacilli. Between April, 1951, and admission to the hospital in late November, considerable clearing of roentgenographic shadows had occurred. Shortly after readmission to the hospital, a regimen of streptomycin-PAS therapy was begun, and two months later resection was performed. The palpable disease was so scattered that the posterior segment of the right upper lobe was removed, and also the small dense nodule in the lower portion of the superior segment of the lower lobe was resected. This tissue contained all demonstrable pulmonary disease.

The calcific nodule measured 4 mm. in diameter and was bone hard. Section of this nodule (Plate XXIV, figure 73), after decalcification, showed a zone of bone and bone-marrow metaplasia about a calcific core. There was no evidence of cellular infiltration in this lesion.

A number of widely scattered, firm yellowish-gray nodules were found in the resected segment. The largest lesion was 7 mm. in diameter and, in part, the content of this focus was soft and crumbly. Acid-fast bacilli were easily found in smears of necrotic debris from two lesions, and cultures of this material gave a growth of two colonies of tubercle bacilli. Microscopic examination of sections from several areas of the segment showed focal parenchymal scars, a few non-necrotic histologic tubercles, and several necrotic lesions (Plate XXIV, figure 72). In a few of the necrotic foci there was a beginning of calcification which was not appreciated either on macroscopic sectioning or on cutting the embedded tissue which had not been decalcified.

The apparent age of the small calcified focus from the lower lobe exceeded that of the disease in the upper lobe by so wide a margin that there could not have been any pathogenetic relation. It seems evident to the writer that in this instance there was a reinfection progressive minimal pulmonary tuberculosis which had behaved in a sluggish manner. In the series of cases under discussion, there was another case of reinfection tuberculosis in which the resected small calcified parenchymal lesion also showed a bony metaplasia and in which the reinfection necrotic lesions showed considerable infiltration with neutrophils.

The cases which have been selected for discussion from the group of 40 patients with clinically "minimal" pulmonary tuberculosis have been chosen to show the considerable variety of morphologic features which have been encountered. Presentation of other cases would be merely repetitious.

The bacteriologic findings in this group will be presented only briefly, as this subject will be discussed in some detail in a later chapter. In only 3 cases were acid-fast bacilli demonstrated in smears of sputum concentrates. One or more cultures positive for tubercle bacilli had been obtained at some time either from sputum or from fasting gastric contents in 24 patients, and in 16 patients no bacilli had ever been demonstrated. All cultures were negative for tubercle bacilli for at least several weeks prior to surgery. In 8 cases many sections of tissue were searched for acid-fast bacilli, with positive results in 6. Smears and cultures were made from the necrotic lesions in 18 cases. Smears were positive for acid-fast bacilli in 15 and cultures were positive for tubercle bacilli in 4 cases. Acid-fast bacilli were found in four-fifths of the cases in which they were sought, and in these cases the numbers of bacilli varied from a very few to large numbers. Growth of tubercle bacilli was obtained in one-fifth of the specimens from which cultures were made. Never more than a few colonies grew, although in several instances large numbers of bacilli were present in the necrotic material which was used for culture.

GENERAL COMMENT

To the clinician and surgeon the minute details dealt with in the discussion of the cases of "minimal" pulmonary tuberculosis may seem to be unimportant. Nevertheless, emphasis must be given to the fact that progressive pulmonary tuberculosis is initiated by a microscopic focus of lobular pneumonia. Without an appreciation of the time-sequence of events between this initial microscopic focus of infection and the discovery of "clinically significant" disease, the problem presented by the tuberculous patient can hardly be properly evaluated. The group of cases which have been discussed clearly show a lack of homogeneity in the development of the progressive disease. In some cases the disease may have been of fairly recent origin, i.e. a duration of several months; and in others a smoldering focus of disease, probably not evident in the chest roentgenogram, had been in existence for several years. These facts would not have been revealed without a meticulous study of the resected specimens. One fact appears indisputable: early tuberculous disease in a clinical sense is not early disease in a pathologic sense. The variety of morphologic features found in the study of "minimal" disease differs from that of disease found in advanced cases only in the amount of lung tissue involved. On this basis it would appear that the problem of "curing" "minimal" pulmonary tuberculosis differs in degree only from the problem of "curing" advanced disease.

From his study of "minimal" pulmonary tuberculosis as found in necropsies on persons who had died suddenly and unexpectedly, the writer became convinced that all patients with clinically minimal disease have necrotic pneumonic lesions and that these would persist even after a long-term course of chemotherapy. This conviction was further established in that the resected tissue in 39 of 40

cases showed necrotic foci. Furthermore, in the necropsy studies both progressive primary and progressive reinfection minimal pulmonary tuberculosis were found. A study of this nature was not possible in the group of cases of resected disease which contained at least 2 cases of reinfection "minimal" disease. However, if the necropsy studies may be used as an indicator, the majority of the patients in the resected group had a progressive primary infection. Neither from the clinical behavior nor from the morphologic features of the resected disease was it possible to differentiate between a primary and a reinfection disease.

The purpose of this study has been to establish pathologic facts relative to pulmonary tuberculosis in living patients. Now that these facts have been elucidated in patients with "minimal" disease, it should be evident that insignificant pulmonary shadows in the superior and posterior portions of pulmonary lobes usually indicate a significant tuberculous lesion even though the etiologic agent cannot be demonstrated. The potentialities of the disease are commonly most difficult to determine promptly and, because of this situation, periodic roentgenograms of the chest, so long as the shadows persist, should be made. Residual shadows seldom represent pulmonary scars only.

It has not been the purpose of this study to foster the idea that all persons with "minimal" pulmonary tuberculosis should be subjected to a major surgical procedure. The decision relative to the management of patients with tuberculosis has been and must remain in the hands of clinicians and surgeons. The function of the pathologist is fulfilled once the nature of the pathologic problem has been elucidated. Known pathologic facts should be carefully considered in the initial consideration of the problem of management of a tuberculous patient. Nevertheless, the writer appreciates that there may be considerations other than the pathology which may shape the course of action.

Of first concern to the clinician and surgeon is the probable effect of chemotherapy upon the lesions of minimal pulmonary tuberculosis. However, there are complicating factors which make it most difficult to obtain a clear-cut answer. When clinical evidence indicates disease of recent origin and pathologic examination of the resected tissues indicates that smoldering disease had been present for several years, it becomes most difficult to determine what effect five months of chemotherapy may have had. A similar complex situation is present when clinical evidence indicates that "minimal" disease has been present for several years and chemotherapy has been given for only two months. It appears that the non-necrotic component of tuberculous disease is favorably affected, for little evidence of this component was found in patients who had received four months or more of chemotherapy. On the other hand, there was pathologic evidence that the non-necrotic component had reacted favorably without chemotherapy. It seems probable that chemotherapy hastens the healing of this component of the disease. The variability in the morphologic picture of necrotic lesions indicates that chemotherapy does not have a significant effect on this component. A discussion of the effect of chemotherapy on the bacilli in necrotic lesions will be deferred to the chapter on bacteriology.

PLATES XXI–XXIV

PLATE XXI

FIG. 63. (× 2) Negro female, age twenty-five, mentioned in text. Represents primary pulmonary tuberculosis of minimal extent.

The necrotic lesion at the top center has undergone considerable liquefaction. Bluish areas are considerably infiltrated with neutrophils.

The necrotic lesions to the extreme right and left show an intact dead lung framework. Although unprovable, these large necrotic lesions probably are the result of endobronchial dissemination. In the necropsy study on cases of sudden death, the writer was unable to find a single instance of two or more minute lesions which could develop into large necrotic lesions located within a limited area of a pulmonary lobe. Contrariwise, several instances were found in which single widely dispersed small foci were found.

There also are a number of smaller foci, some of which are necrotic, some are tubercles, and an occasional one is a small area of recent lobular pneumonia. All demonstrable pulmonary disease was contained within the volume of lung illustrated. Two lymph nodes in line of drainage were partly occupied by necrotic lesions. These nodes were freely movable.

FIG. 64. (× 2) White male, age thirty-five, mentioned in text. Primary minimal pulmonary tuberculosis.

The large necrotic lesion has a well-formed dense fibrotic periphery. The lung structure of the necrotic area is partly disintegrated, and the hole in the central area represents small cavity formation. This tissue was fixed *en bloc* before it was cut. Numerous small endobronchial disseminations may be seen. Some are necrotic, some are "tubercles," and an occasional one is a small focus of lobular pneumonia. The section represents the extent of the tuberculous disease in the lungs. A single lymph node in line of drainage showed a single 2 mm. necrotic lesion.

FIG. 65. (× 2) White male, age fifty-three, mentioned in text. Reinfection minimal pulmonary tuberculosis. The disease was located in the superior portion of the posterior segment of the right upper lobe. In the right lower lobe a 2 mm. densely calcified parenchymal lesion was found near the diaphragm, and two small densely calcified lymph nodes were adjacent to the lower lobe bronchus.

The section shows the entire extent of the minimal pulmonary tuberculosis. A large block of lung was fixed in 10 per cent formalin before it was cut. The largest necrotic lesion shows that a part of the necrotic pneumonic area has been liquefied and sloughed. The remaining necrotic tissue is infiltrated to a variable degree with neutrophils. The remaining lesions are regarded as endobronchial disseminations.

These 3 cases illustrate unhealed minimal pulmonary tuberculosis of different ages as found in the necropsy study of cases of sudden and unexpected death. In no instance was disease of minimal extent found which did not show multiple lesions. This applies also to the small number of cases in which the minimal disease was represented only by calcified foci and parenchymal scars.

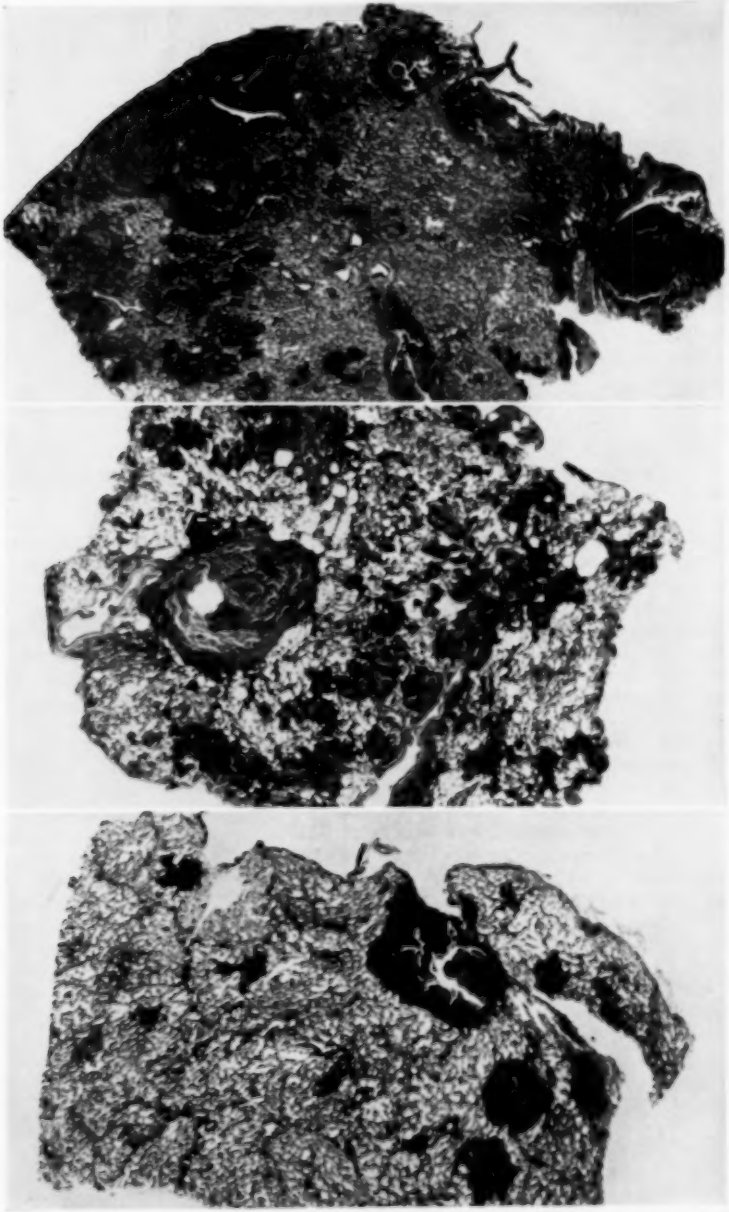


FIG. 63

FIG. 64

FIG. 65

PLATE XXI

PLATE XXII

FIG. 66. (× 10) White male, age twenty-seven. Case discussed in text. The smallest necrotic lesion at the top has an old hyalinized fibrotic periphery. The middle-sized necrotic lesion below it has a more cellular fibrotic periphery which is somewhat infiltrated with lymphocytes. The dark, somewhat broken-up inner portion is a zone of rather dense calcification. The largest lesion has a thick actively forming fibrotic periphery which is heavily infiltrated with lymphocytes. The inner edge of this zone is composed of necrotic tissue which is irregularly infiltrated with neutrophils. The broken central portion which partly fills the cavity space is composed of necrotic debris and neutrophils. No lung structure is present in this area.

The significant features of these three lesions is that they are of different age, of different morphology and, from the serial section study, were found to connect one with the other. The smallest focus is interpreted as the oldest lesion; the focus with calcification is next in age; and the cavitary lesion is the more recent lesion.

The bronchus in the lower left quadrant is distended with mucus. This condition is due to the involvement of the bronchus, at a different level, in the scar forming about the cavitary lesion. A branch of the bronchus in the lower edge, 4 cm from the right edge of the illustration, connected openly with the cavity at another level.

FIG. 67. (× 5) White male, age twenty-seven. Case discussed in text. Three of the six necrotic lesions are shown. After dehydration the largest lesion was cut across to ensure thorough impregnation with paraffin preparatory to serial sectioning. The lung framework of this lesion was sufficiently broken down so that many pieces fell out during the remainder of the processing. The blue color in the central portion of all lesions is due to infiltration of neutrophils. Each of the six separate lesions had a well-formed periphery of fibrous tissue, and in each one or more patent small bronchioles were found within the fibrotic zone. In the periphery of the fibrotic zone, there was a variable degree of lymphocytic infiltration, the small blue foci easily seen in the illustration. In two lesions, not present in the illustration, an intense infiltration of eosinophils was noted in the outer portion of the fibrotic zone.

FIG. 68. (× 4) Oriental male, age twenty-six. Case discussed in text. There are two necrotic lesions in the left half of the picture. The larger one shows foci of a bluish color. These are areas infiltrated with neutrophils. The smaller necrotic lesion is slightly above and to the left. The remainder of the lesions are "tubercles" in which giant cells are numerous. Several of these lesions are so thoroughly fibrosed that only an occasional giant cell remains. Others show no evidence of fibrotic organization. Apparently these small endobronchial disseminations are of different ages.

This specimen was resected two months after streptomycin-PAS therapy was instituted. It is most unusual to find "tubercles" in specimens resected after more than four months of combined chemotherapy, unless an open cavity is present.

In this case the minor component was the necrotic lesions. Lesions of this nature remain regardless of the length of time chemotherapy is given. On the other hand, the non-necrotic component will heal completely, leaving behind numerous parenchymal scars.

FIG. 66

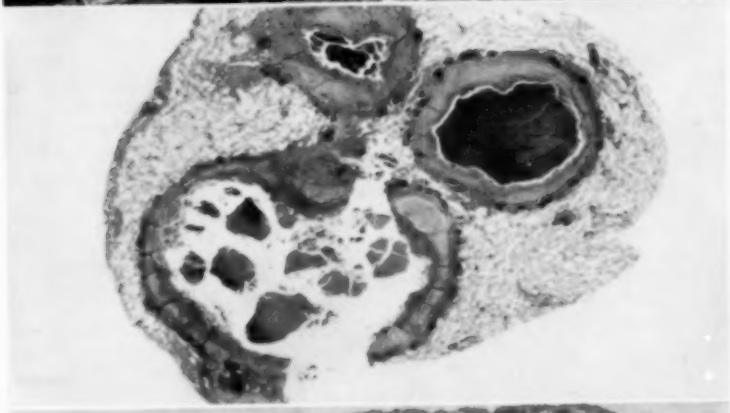


FIG. 67

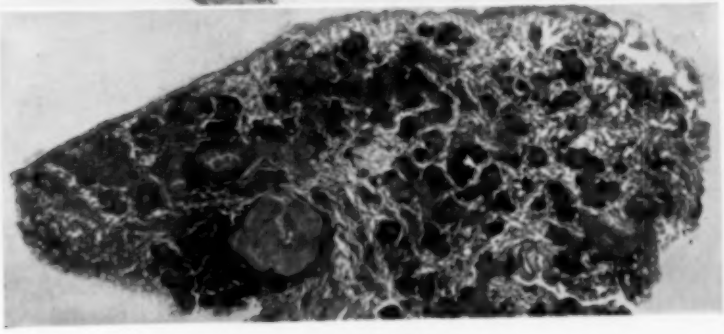


FIG. 68

PLATE XXII

PLATE XXIII

FIG. 69. (× 3) White female, age twenty. Case discussed in text. All of the numerous lesions are represented in the several sections of tissue. The lesions consist of necrotic lesions, parenchymal scars, and an occasional organizing "tubercle." No lesions of recent origin were found. Some of the necrotic lesions are undergoing liquefaction; these show bluish areas of neutrophilic infiltration within the necrotic zone. Others show no evidence of liquefaction. The large necrotic lesion in the upper left corner is a partly filled-in cavity. Within this lesion a 1 mm. dense calcific focus was found which probably represented the initial tuberculosis focus.

The round hole in the lesion in the lower central portion of the section of tissue to the right is the bronchus which connected with the cavity in the upper left-hand corner of the illustration. A major portion of the bronchus is necrotic and contains necrotic debris.

This specimen shows a pathologic picture which is encountered not infrequently in specimens resected six months or longer after the institution of combined chemotherapy.

FIG. 70. (× 15) White female, age twenty-five. Case discussed in text. The small amount of tissue removed showed only parenchymal scarring and the three necrotic lesions in the illustration. All palpable disease was resected. The three lesions represent a sequence of events similar to that present in figure 66. The smallest lesion measured less than 1 mm. in diameter. It was well hyalinized and contained a considerable deposit of anthracotic pigment. On morphologic grounds, it is the oldest lesion and probably is the initial focus from which the other lesions arose through endobronchial sloughing. The largest lesion measured 4 mm. in diameter, and a bronchial connection with this lesion was found by fine wire probe. The central blue area is a mixture of neutrophils and necrotic debris with no evidence of lung structure. Note the red necrotic inner portion of the fibrotic periphery. This lesion is a filled-in cavity.

FIG. 69

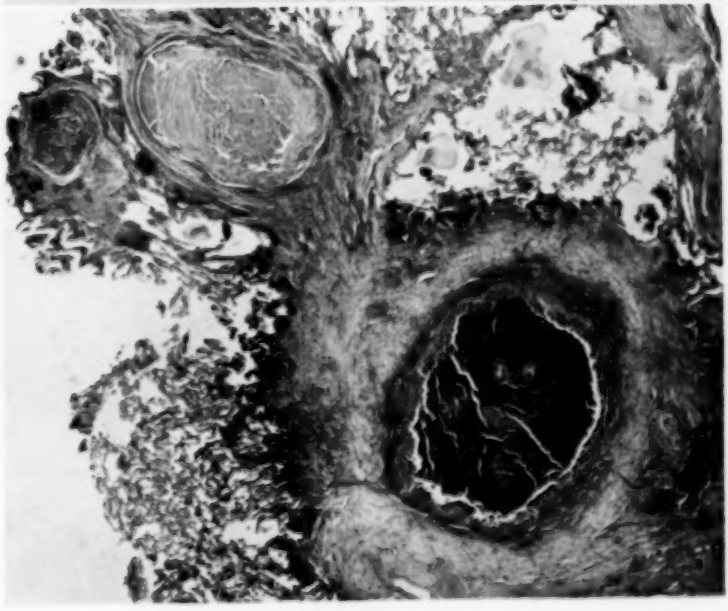


FIG. 70

PLATE XXIII

PLATE XXIV

FIG. 71. (× 15) White male, age twenty-three. Case is discussed in text. The illustration is one of three consecutive sections which showed the bronchial connection with the necrotic lesion. The connecting bronchus is a branch of the larger bronchus which lay adjacent to the lesion (left center near the periphery of the illustration). The epithelium of the connecting bronchus was intact for a short distance, and beyond this all tissue was necrotic. The clear channel into the necrotic central portion represents the course of the bronchus. There is a considerable comminution of the dead lung framework in the central portion. The delimiting peripheral fibrotic zone is not as completely formed as it is in the largest lesion in figure 70.

Note in the upper left quadrant, within the large lesion, a small focus which has a well-formed fibrotic capsule of its own. This small lesion is 3.5 cm. from both the left and the upper edges of the illustration. The necrotic contents of this focus is considerably infiltrated with neutrophils, and the lung framework is well disintegrated. This lesion became an integral part of the larger necrotic area at a different level. This small lesion was less than 1 mm. in diameter. It is probable that this is the initial focus which, through sloughing, gave rise to the larger lesion, which also was undergoing liquefaction. The four small necrotic foci and several parenchymal scars in the surrounding lung tissue indicate that some sloughing from the larger lesion already had occurred.

Resection was done three months after multiple-drug therapy was started.

FIG. 72. (× 4) White female, age thirty-five. Case discussed in the text. The largest necrotic lesion shows some disintegration of the dead lung framework. The blue areas in the periphery of the fibrotic "capsule" are collections of lymphocytes—a common finding. The two small necrotic lesions have foci of calcification and would seem to be older foci. Three small organizing "tubercles" are present as well as small focal parenchymal scars which are regarded as healed "tubercles." The wide separation of the lesions in the segment and the different ages of lesions suggest that the disease had progressed in a sluggish fashion for a number of years. No evidence of active sloughing or of liquefaction of necrotic lesions was found.

FIG. 73. (× 15) Same patient as above. Section of densely calcified parenchymal lesion from lower lobe which was evident in the first chest roentgenogram which was taken twelve years previously. Considerable metaplasia to bone and bone marrow had occurred peripheral to the rocklike central calcified portion. This would seem to be an ancient, completely healed primary parenchymal lesion which probably long antedated the first chest roentgenogram.

This case is offered as evidence of a reinfection minimal pulmonary tuberculosis in a young adult. This situation was found in the necropsy study reported in a previous chapter. However, in that study the large proportion of cases of reinfection tuberculosis was found in adults and in males more than forty years of age.

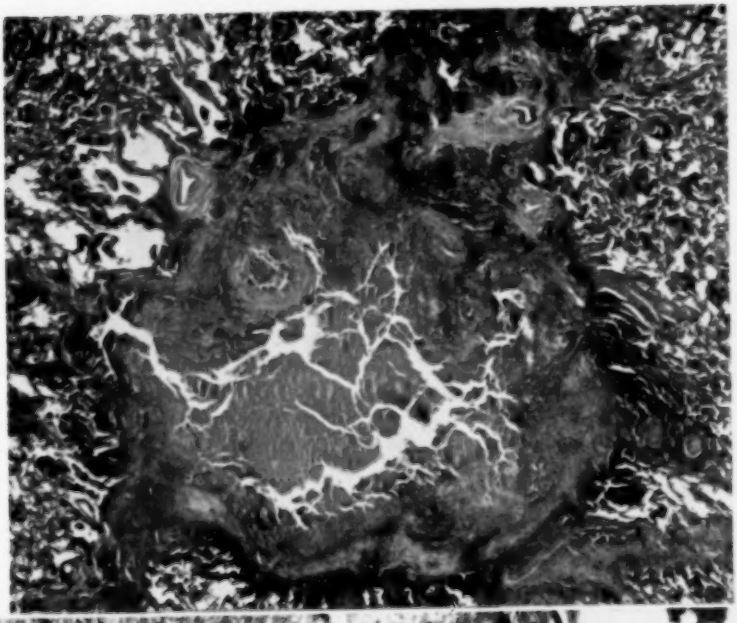


FIG. 71

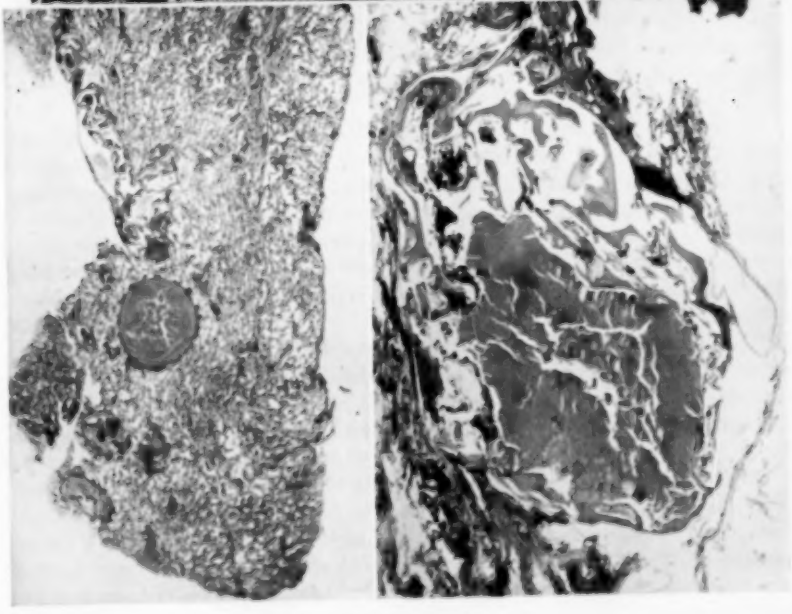


FIG. 72

FIG. 73

PLATE XXIV

CHAPTER VII

BRONCHIAL LESIONS IN TUBERCULOSIS

Although the bronchial tree makes up only a minor portion of the volume of the lung, it is indispensable for the passage and the cleansing of air. In tuberculosis it becomes the channel through which the liquefied necrotic tissue from parenchymal lesions is discharged. Unfortunately, it also serves as the disperser of the sloughing debris into hitherto uninvolved lung parenchyma, and in this manner serves as a propagator of progressive disease. In these circumstances the bronchi themselves become affected, to a greater or lesser extent, by the disease process. It will be the purpose of the present discussion to indicate the degree to which bronchi are affected in pulmonary tuberculosis and to describe the behavior of bronchial lesions.

In the study of experimentally produced tuberculosis, it was found that necrotic lesions commonly included bronchi which, during the process of liquefaction and sloughing, became the major source from which the disease was disseminated within the lung. It was also found that, in vaccinated reinfected animals, the prolonged survival of the animals affords an opportunity on occasion for a clean slough of the necrotic bronchial lesion and a covering of the clean surface of the ulcer by squamous epithelium. Beyond these two features there was nothing which could serve as a guide in the study of bronchial lesions in the human lung.

At necropsy on tuberculous patients, the tracheal and bronchial mucosa frequently have been observed to be in a thickened and congested state; however, ulceration, such as that found quite often in the gut, has not been a common occurrence. Focal destruction of an entire bronchial wall has been, in the writer's experience, an unusual finding. When found, it apparently has resulted from an extension of the necrotizing and sloughing process from an underlying tuberculous bronchial lymph node. Such a situation has been observed sometimes in infants, but rarely has it been seen in adults.

In two instances only, in the writer's experience, has death from a sudden massive hemorrhage been found to have been caused by a rupture of a large vessel through a bronchial ulcer (Plate XXV, figure 74). In these two instances it appeared that both the bronchus and the vessel had become involved in the necrotizing process which was an extension of the disease from a necrotic lymph node. Bronchi and large vessels are intimately associated with hilar lymph nodes. Hence, it would seem that this condition would be found more often if the focal destruction of bronchial walls were induced frequently by an extension of tuberculous disease beyond the confines of a necrotic lymph node. The writer has not seen an extension of a necrotic mucosal ulcer of larynx, trachea, or bronchus into underlying tissue. Three cases have been seen in which an extensive mediastinal

tuberculosis was associated with, and probably was caused by, necrotic lymph node disease. All 3 patients died from a generalized miliary tuberculosis. In these cases no penetrating ulcers of the trachea or bronchi were found. It was common to find several bronchial communications to large cavities in cases of extensive cavitation. This would suggest that considerable portions of the bronchial tree of a lobe had been liquefied and expectorated. Marked stenosis of a large bronchus has been seen but, in the writer's experience, such a finding has been unusual.

In a study of pulmonary tuberculosis in cattle at slaughterhouses, the writer observed focal mucosal ulcerations of trachea and bronchi not infrequently. This condition was found more often in advanced disease. One of the most useful means of identifying the oldest sloughing lesion in bovine pulmonary tuberculosis was the increase in the number of bronchial ulcers as the oldest lesion was approached. Owing to the sturdiness of bronchial structures and to the larger size of bronchi, this process was much more easily observed macroscopically in the bovine than in the human lung.

In bovine tuberculosis, regardless of the amount of parenchymal disease, necrotic tuberculous lymphadenitis was a prominent feature. The infected nodes sometimes attained the size of hens' eggs, and no evidence was found by the writer that the bronchi were compressed by the enlarged nodes or that bronchial ulceration was induced by extension of the lymph node tuberculosis through a bronchus. However, the cases of advanced disease comprised only a minor portion of the 500 pairs of tuberculous bovine lungs which were examined. A study of a much larger number of cases of advanced disease would be required if a comparison with the situation found in advanced human pulmonary tuberculosis were to be made.

OBSERVATIONS ON RESECTED SPECIMENS

As the material available for morphologic study was removed from patients who were carefully selected by the clinicians and surgeons, the data obtained from the study of the specimens is somewhat biased. For instance, in the group there were 19 (6 per cent) specimens in which macroscopic evidence of stenosis of a large bronchus was found. In the writer's experience, a considerably lower incidence of stenotic bronchi is found at necropsy on tuberculous patients.

The most common bronchial lesion (Plate XXV, figure 75) found in the resected specimens was a considerable degree of lymphocytic infiltration of the mucosa with or without congestion and edema. This condition caused a thickening of the mucosa and, consequently, a narrowing of the bronchial lumen. The epithelial lining of these bronchi usually was intact and normal. Mucosal lesions were found invariably in bronchi which were draining sloughing lesions. In specimens in which filled-in cavities were present and the larger bronchial branches contained no secretions, it was unusual to find more than a light sprinkling of lymphocytes in the mucosa. However, sections of the bronchus near to its connection with the filled-in cavity commonly showed considerable lymphocytic infiltration of the mucosa, and sometimes necrotic debris was present in the lumen. From these observations it would appear that, with a cessation of slough-

ing, the bronchial mucosa returned to a normal condition. In other words, the condition was completely reversible.

Not infrequently histologic tubercles and giant cells were associated with the lymphocytic infiltrations of the nonulcerated mucosa. These lesions were found more often in smaller bronchi, well out in the lung parenchyma, than in the larger bronchi near the point of resection. On occasion tubercles and giant cells in considerable numbers (Plate XXV, figure 76) were found in the mucosa. In these bronchi there was no evidence of ulceration, and rarely was there evidence of necrosis in the tubercle. On occasion focal scars (Plate XXV, figure 77) in the mucosa were found in larger bronchi which had normal intact epithelial linings. These focal scars were considered to represent healed tubercles. This interpretation is in keeping with the behavior of the histologic tubercle as described in the preceding chapter. It would appear that the mucosal tubercles represent an implantation infection from the sloughing material within the bronchi rather than from the lymphatic system. It would seem highly improbable that tubercle bacilli would be shunted from the larger lymph vessels which lie in the periphery of the bronchus to the minute lymph vessels of the mucosa.

In the thousands of tissue sections studied by the writer, there was only one instance (Plate XXVI, figure 78) found of a focal mucosal ulceration which, beyond question, was caused by a necrotic mucosal lesion eroding through the overlying epithelium. Hence, it would appear that focal necrotic tuberculous mucosal lesions rarely occur in human pulmonary disease, for no evidence has been found to suggest that chemotherapy significantly affects a necrotic lesion once it is formed. The rarity of focal necrotic mucosal ulcerations in man is in sharp contrast to the findings in bovine pulmonary tuberculosis. Evidently, in human beings, focal tuberculous infection of the bronchial mucosa cannot be regarded as the common cause for necrotic endobronchial disease.

As necrotic parenchymal tuberculous lesions commonly involve rather large areas of lung tissue, one would expect to be able to demonstrate bronchial structures within the lesion. Dead vessels and alveolar walls commonly can be demonstrated; however, positive identification of bronchial walls has proved to be difficult. This may be due to the delicate structure of smaller bronchi. On occasion a small piece of cartilage (Plate XXVI, figure 79) may be found deep within a necrotic lesion. As, in smaller bronchi, bits of cartilage usually occur only at the point of bifurcation, it is evident that cartilage will be found only occasionally in random sections of lung parenchyma. For example, in the examination of 400 serial sections obtained from a 1 cm. necrotic parenchymal lesion, a small bit of dead cartilage was found deep within the lesion in three consecutive sections only.

BEHAVIOR OF NECROTIC ENDOBRONCHIAL TUBERCULOSIS

In the specimens resected from 295 tuberculous patients, macroscopic evidence of stenosis of the bronchi was found in 19 cases and, in addition, necrotic endobronchial tuberculosis was found microscopically in 30 cases. Thus, necrotic ulcerative endobronchial disease was found in only one-sixth of the cases. All

necrotic endobronchial tuberculosis which was observed in the larger bronchi was associated with some degree of stenosis. This suggests that specimens had not been removed in the early stages of necrosis. It was found that the presence of necrotic endobronchial disease in small bronchi could be determined with certainty only on microscopic examination. Often a small bronchus with a thickened wall and a narrowed lumen showed only congestion, lymphocytic infiltration and tubercles in the mucosa, and an intact normal epithelial lining. This was the condition found not infrequently in larger bronchi which served as the route of drainage from a sloughing parenchymal focus.

The earliest phase of necrosis of a bronchus was observed rarely; when found, it was in a bronchus (Plate XXVI, figure 80) which was directly connected with a necrotic parenchymal lesion of fairly recent origin, as judged from the morphologic appearance of the fibrotic periphery. These early necrotic lesions were limited to the mucosa, and necrotic material was invariably present in the bronchial lumen. There was no evidence of histologic tubercles or giant cells in the bronchial wall beyond the mucosa. Just peripheral to the necrotic area was a dense infiltration of lymphocytes, and peripheral to that was an actively forming zone of fibrous tissue. The area of necrosis was joined to the necrotic parenchymal focus, and in the remainder of the bronchus there was a normal epithelial lining. This localized bronchial lesion probably represents the early phase of necrosis of the mucosa.

Extensive necrotic endobronchial disease was present in two specimens in the entire series, and in both of these there was a partial stenosis of a large bronchus at the hilum of the lung. In considerable areas large bronchial branches showed a complete sloughing of the bronchial wall with absence of cartilage. The relationship of these lesions to sections from other areas, to vessels peripheral to the lesion, and the elongated shape of the lesions suggested that they were bronchi, even though the entire bronchial wall was absent. In other sections (Plate XXVII, figure 81) pieces of cartilage were found which were directly involved in the necrotic process, and in some of the lesions there were areas in which islands of a normal ciliated epithelium were found. These bronchi were filled with exudate which in places was composed in large part of neutrophils and, in other areas, of necrotic debris without recognizable cells. Beyond the exudate there was a relatively thin zone of necrosis, and beyond this there was an actively forming fibrotic zone. The process as a whole was very similar to a cavity wall, and it appeared that the condition had existed for a considerable time. No evidence of healing was found.

In some cases only an occasional bronchus was found to have extensive necrotic endobronchial disease. This situation was present in a lobe which was resected after it had been under thoracoplasty for fifteen years. The inner portion of the bronchial branch which served as a drainage canal of an open slitlike cavity was entirely necrotic (Plate XXVII, figure 82) from its point of origin to a junction with the open cavity. The larger bronchus from which the branch to the cavity arose showed only a considerable lymphocytic infiltration and an occasional histologic tubercle or giant cell proximal to the point of bifurcation. The second

branch of the bifurcation showed only extensive lymphocytic infiltration of the mucosa.

This situation suggests two things. First, extensive necrotic endobronchial disease can remain localized to a single bronchial branch which lies well beyond the area which can be viewed at bronchoscopy. Second, necrotic endobronchial disease may remain for years in an unhealed state. Necrotic endobronchial disease presents a situation which is similar to the problem of healing of parenchymal cavities.

Once necrosis, either of the bronchial mucosa or of the entire bronchial wall, had occurred it was evident that healing could occur only by a clean slough of the necrotic tissue. Inasmuch as complete healing was observed only rarely, a clean slough would seem to be quite uncommon. The evidence of healing which was found most frequently was bronchial stenosis (Plate XXVII, figure 83)—a marked fibrotic thickening of the bronchial wall which surrounded a greatly reduced central necrotic area. In only two instances was a complete occlusion of the bronchus by scar tissue found. In one instance a bronchus (Plate XXVII, figure 84) which was identified by the presence of a small piece of cartilage was completely closed by scar tissue in the midst of which was a portion of gland filled with retained mucus. The other specimen was obtained from serial sections of a small filled-in cavity to which a patent bronchial connection had not been found by probe. Study of the serial sections showed a complete occlusion of the bronchus (Plate XXVIII, figure 85) by scar tissue for a short distance proximal to the cavity. The patent bronchus proximal to the occlusion showed a mild degree of lymphocytic infiltration, an occasional histologic tubercle in the mucosa, and a normal ciliated epithelial lining.

A few small bronchi (Plate XXVIII, figure 86) with necrotic ulceration were observed in which a portion of the necrotic tissue had been sloughed cleanly, and squamous epithelium had covered the clean granulating surface to a greater or lesser extent. In only two instances was a complete lining of stratified squamous epithelium found. In addition to the findings discussed above, further evidence derived from the resected specimens indicated that a bronchus with a healed necrotic lesion more often remained patent, due to an outgrowth of squamous epithelium over the cleansed surface, than completely occluded by scar tissue.

BRONCHIAL LESIONS BEYOND A STENOSIS

Of particular interest in this study was the condition of bronchial branches beyond a stenotic lesion. In more than half of the resected specimens in which stenosis of a major bronchus was present, the stenotic lesion either was not included in the specimen or it had been gripped so firmly by forceps during operation that a satisfactory study of the area of stenosis was not possible. In eight specimens, however, a careful microscopic study was possible. All of these showed a patent lumen which was surrounded by a necrotic zone even though in some specimens the opening was too small to be demonstrated by probe.

In one specimen the inner surface of the stenotic bronchus (Plate XXVIII, figure 87) was covered in part by stratified squamous epithelium. This specimen

came from a white female patient who had a diagnosis of advanced tuberculosis at the age of twenty-two years. During the ensuing six years the clinical course was marked by several exacerbations of disease. Bronchial stenosis was suspected, but confirmation of the stenosis by bronchoscopy was proved only a short time before surgery. Microscopic study of the specimen showed that all bronchial branches (Plate XXVIII, figure 88) beyond the stenosis were filled with exudate and had rather large areas of necrotic endobronchial disease. There was no evidence in the branch bronchi of an outgrowth of stratified squamous epithelium from areas in which a normal epithelial lining was present. The lung parenchyma in this portion of the lobe was airless and showed little evidence of fibrosis or of necrotic parenchymal lesions. The remainder of the lobe was air-containing and showed numerous necrotic parenchymal lesions without evidence of necrotic bronchial lesions.

Another case of advanced disease of several years' duration also showed marked stenosis of two segmental bronchi (Plate XXIX, figure 89), and the bronchial branches distal to the stenotic area were filled solid with necrotic debris. In the branch bronchi the walls were completely necrotic and a peripheral fibrotic zone was present.

Another specimen showed marked stenosis at the point of origin of all basal segmental bronchi of a lower lobe, with the segmental bronchus to the superior segment uninvolved and normal. This lobe was removed from a patient who had been hospitalized and was discharged from an institution ten years previously as having arrested tuberculosis. During the period after discharge the patient was well clinically; however, on occasion acid-fast bacilli were found in the sputum. At the end of this period, bronchography showed marked stenosis of the lower lobe bronchus. At surgery the lobe was found well aerated and would not collapse. Microscopic study showed the anterior basal segment to be airless and to have extensive parenchymal scarring and numerous necrotic parenchymal lesions. The entire bronchial tree of this segment was filled with necrotic debris, and the bronchial walls were all necrotic. There also was a considerable necrotic endobronchial disease of the other segmental bronchi just distal to the areas of stenosis. However, these segments were all fully aerated but were not emphysematous. Only an occasional small necrotic parenchymal lesion and a few parenchymal scars were observed in these segments. The superior segment, bronchial tree, and parenchyma were normal except for an occasional small necrotic parenchymal focus and scar. It would appear that the aerated condition of all but one of the basal segments was due to the passage of enough air from the parenchyma of the superior segment into the parenchyma of the basal segments to permit full aeration. Evidently the communications between the superior segment and the remainder of the lobe were so slight that only a slow passage of air was possible, thus preventing a collapse of the lobe either during surgery or after resection.

In still another specimen a marked stenosis of a small bronchus was found well beyond the hilar region. Distal to the point of stenosis the bronchi (Plate XXIX, figure 90) were markedly distended with a mixture of mucus and necrotic exudate,

and focal areas of necrotic endobronchial disease were present. This lesion was firm with a consistency resembling that of a necrotic parenchymal lesion. A considerable amount of parenchymal scarring and a few small necrotic praenchymal lesions were present in the remainder of the tissue which was removed.

The situation found in the cases selected for discussion indicates the variability which may be encountered both in bronchi and in the lung parenchyma distal to a stenosing bronchus. The common feature in all of the specimens was the presence of necrotic endobronchial disease beyond the area of stenosis. There was, however, a very great difference in the amount of necrosis. In some instances the bronchi were markedly distended with retained secretions, and in other instances they were not. The distended bronchi could be called bronchiectatic, but it would seem preferable to use the term dilatation of bronchi distal to stenosis. It is unlikely that bronchi beyond a stenosis can be outlined by bronchography because of the stenosis and also because the bronchi are already filled with secretions. If the specimens which the writer has had the opportunity to study may be taken as a representative sample, then it would appear that stenosing bronchi commonly do not become completely occluded by scar tissue.

THE DIFFICULTY OF IDENTIFYING SMALL NECROTIC BRONCHI

Careful study of small round, oval, or elongated necrotic tuberculous lesions sometimes shows the necrotic area to be granular without evidence of parenchymal structure. These lesions often are discrete nodules. The writer has long suspected that lesions of this nature are bronchi in which a dispersed plug of necrotic debris had lodged. However, seldom is proof found that such lesions may represent bronchi involved for only a limited distance.

In studying the resected specimen, six nodules were observed which proved to be necrotic lesions that involved the entire bronchial structure for a short distance only. A piece of cartilage was found in direct association with all but one of the lesions. In three instances a piece of necrotic cartilage (Plate XXVI, figure 79) was found in the midst of the necrotic area, and in two others the cartilage was peripheral to the necrotic zone. In one specimen the surgeon had dissected out a branch bronchus which extended approximately 5 cm. from its point of origin and, 3 cm. from its point of origin, there was a firm spherical nodule which measured 4 mm. in diameter. The bronchus gave the appearance of a string with a bead on it. With gentle manipulation a small, easily bent, piece of copper wire was easily passed through the entire length of the bronchus and on its way passed through the firm nodule. On cross-section the nodule was firm throughout and was of a yellowish-gray color. A block of tissue was taken which included this nodule (Plate XXIX, figure 91), and another block of tissue contained the bronchus proximal to the nodule. On microscopic study the central necrotic portion of the lesion showed a slitlike opening and an amorphous central structure with focal areas in which a rather large amount of nuclear dust was present. In the periphery there was a cellular fibrotic zone. The section of the bronchus proximal to the lesion showed an intact normal ciliated epithelial lining, and in the mucosa a considerable amount of lymphocytic infiltration and an occasional

small histologic tubercle were found. It would appear that the lesion resulted from the lodgment of a small plug of dispersed necrotic debris in the lumen of the bronchus.

From these few remarks, it seems apparent that small discrete necrotic bronchial lesions can arise from pieces of dispersed necrotic debris which lodge in the lumen. How frequently this may happen it is impossible to state; however, lesions of this nature may well occur more often than has been thought. Liquefaction of a necrotic lesion of this type would tend to spread the tuberculous infection. An organization by scar formation would cause a local stenotic lesion beyond which bronchi could become distended with retained secretions.

RELATION OF BRONCHI TO NECROTIC PARENCHYMAL LESIONS AND CONDITION OF CONNECTING BRONCHI

The writer was taught that necrotic or "caseous" lesions which showed an encircling fibrotic periphery or "capsule" were entirely sealed off and so were innocuous. Formerly these lesions were commonly regarded as obsolete and healed. The writer also was taught that the disease was slowly propagated by the penetration of bacilli through the peripheral fibrosing area during the growth of the early lesion and that in this manner the "tuberculoma" was formed. Lesions of this nature also were closed and had never had a bronchial connection. If endobronchial dissemination occurred from such lesions, then it was an accident which was caused by a rupture of the capsule through the wall of an adjoining bronchus. This focal dissolution of the capsule was commonly attributed to either a focal tuberculin reaction or to the occurrence of an acute upper respiratory infection in the area.

In the preceding chapter it was shown that even old necrotic lesions can liquefy and slough and that filled-in cavities usually have patent bronchial communications. It would seem necessary to determine the actual microscopic relationship of bronchi to necrotic parenchymal lesions.

In the group of resected specimens, the writer was always able to demonstrate by probe a patent communication between an open cavity and one or more bronchi. No special effort was made to get sections for microscopic study through the bronchocavitary junction. However, on a number of occasions a communication between bronchus and cavity was seen in random sections. Microscopic study showed bronchial communication with either unsloughed lesions or filled-in cavities in 80 of 295 cases. In 28 of these cases, stratified squamous epithelium was found to a greater or lesser extent at the area of junction. The bronchial connection was found in random sections in 72 cases. In 4 cases of minimal pulmonary tuberculosis, the entire area of disease was serially sectioned, and in 3 a direct bronchial communication was revealed by microscopic study. In four specimens serial sections were made of blocks of tissue which contained bronchi which had been probed without success for a bronchial connection. Microscopic study of these sections showed patent bronchial connection in three and a bronchus which was found to be completely closed by scar tissue in one.

The situation found in three of the four serially sectioned minimal disease

specimens has already been presented in the chapter on resected minimal tuberculosis. The fourth specimen contained a firm lesion which measured 1.2 cm. in diameter. A small bronchus was found in the resected surfaces of the specimen, and a probe inserted into this bronchus failed to show any bronchial connection with the lesion. From this block of tissues, 400 sections, each 30 micra in thickness, were obtained and no sections were lost. Microscopic study of these sections showed a large necrotic focus and seven separate small necrotic lesions. The largest of the small foci showed a minute patent bronchus which could be traced through the fibrotic periphery to the necrotic zone. No bronchial connections were found in the other small lesions.

The large necrotic parenchymal lesion (Plate XXX, figure 92) showed bronchial openings through the peripheral zone of fibrosis in only nine of the 400 sections. Two different bronchial branches were connected with the lesion. The aperture of one bronchus extended through only three sections and of the other through only six sections. The smaller bronchus (Plate XXX, figure 93) was lined with squamous epithelium from its point of origin from a bronchial branch with ciliated epithelium. This latter bronchus was completely separate from the necrotic lesion. The squamous epithelial lining of the smaller bronchus extended through the fibrotic capsule and over its inner surface up to the point at which there was no separation between living and dead tissue. This small bronchus was surrounded by scar tissue in which an occasional histologic tubercle was present. It would seem that the wall of this small bronchus had undergone necrosis; that the necrotic tissue had completely sloughed; and that subsequently a metaplastic outgrowth of epithelium from the parent bronchus had re-covered the clean inner surface of the bronchial lumen and a portion of the clean inner surface of the fibrotic zone which surrounded the necrotic lesion. The larger bronchus (Plate XXX, figure 94) showed a ciliated epithelial lining through the fibrotic capsule, and then squamous epithelium covered the inside of the fibrotic tissue up to the point at which there was no separation between living and dead tissue. A continuous sheet of squamous epithelium extended from one bronchial opening to the other and covered the clean inner surface of the fibrotic capsule to an extent of 10 sq. mm.

The large necrotic lesion was made up of several areas of tuberculous pneumonia, some of which had a periphery of necrotic fibrous tissue. This would indicate that the lesion as a whole contained pneumonic lesions of different ages. The only portion of the lesion in which a liquefaction of the dead tissue had occurred was in the portion contiguous with the area in which epithelization was found. In this region the fact that some areas were heavily infiltrated with neutrophils indicated that the process of liquefaction was still in process. The presence of the small independent necrotic foci would suggest that some endobronchial sloughing had occurred. During the entire period of observation, only a single gastric culture positive for tubercle bacilli was obtained, and this happened shortly after the lesion was discovered.

The difficulty of demonstrating bronchial connections with necrotic parenchymal foci is well shown by this specimen. In spite of the presence of two bronchial

connections, only nine of the 400 serial sections showed the connections. The lesion had all of the morphologic characteristics of a "tuberculoma." The evidence at hand does not suggest that the bronchial communications were formed by the rupture of a "closed" parenchymal lesion through a bronchial wall. Deep within this lesion a bit of dead cartilage was found, a fact which argues against the lesion's enlarging simply by expansion of the disease through the peripheral fibrotic capsule. To the writer it seems evident that bronchi are an integral part of a pneumonic lesion which undergoes necrosis and that there usually is no sealing off of the proximal portion of the bronchus at the point at which necrosis of the lesion stops. However, the connecting bronchus probably is often effectively plugged, at least until considerable liquefaction of the dead tissue has taken place.

In another specimen a block of tissue was serially sectioned because a bronchial connection with a solid necrotic lesion had been found by probe. Study of the sections showed a direct bronchial connection with the necrotic lesion. The bronchus (Plate XXXI, figure 95) for an appreciable distance proximal to the lesion had undergone necrosis, even to the extent that cartilage was involved, and a considerable amount of the necrotic tissue had sloughed. However, little evidence was found that the necrotic bronchial walls had been re-covered by epithelium. The necrotic pneumonic lesion in this case showed extensive areas which were heavily infiltrated with neutrophils, and in these portions of the lesion there was a complete disintegration of the dead framework of the lung parenchyma. The bronchus leading to the lesion was filled with purulent exudate. The disease in this case was discovered nine months prior to resection, and multiple-drug therapy had been given for seven months.

The most marked growth of stratified squamous epithelium at the junction (Plate XXXI, figure 96) between a bronchus and a filled-in cavity was found in a specimen removed from a patient who had been under treatment for tuberculosis for seven years prior to resection. A thoracoplasty had been done two years prior to resection, and only a few doses of dihydrostreptomycin were given prior to surgery. This specimen showed a large area of necrotic tuberculous pneumonia, only a part of which had liquefied and sloughed.

GENERAL COMMENT

In the preceding pages the writer has attempted to describe the changes observed in the bronchi in pulmonary tuberculosis and to discuss briefly the significance of these findings. The most frequent bronchial lesion is lymphocytic infiltration of the mucosa, with or without congestion and edema. The bronchitis probably is a reaction to the irritating effect of sloughing necrotic material and apparently disappears completely when the process of sloughing stops. The next most frequent lesions are histologic tubercles and giant cells in the bronchial mucosa. The evidence indicates that lesions of this nature are caused by implantation in the mucosa of tuberculous infection which is carried in the sloughing necrotic debris. They heal characteristically as minute scars. On rare occasions, once in this study, an implanted tuberculous focus may proceed to necrosis

with ulceration of the overlying epithelial covering, thus forming a focal ulcerative lesion.

Much less often necrosis of the mucosa and even of the entire bronchial wall occurs. When this happens it is a serious affair which leads to stenosis, usually without complete closure, of the affected bronchus and to retention of exudate and secretions distal to the stenosed area. Frequently, although not always, the bronchi beyond the stenosis become distended with retained material.

To describe this situation the writer prefers the term *dilatation of bronchi distal to obstruction* rather than the term *bronchiectasis*. The relationship between tuberculosis and bronchiectasis will be discussed in the following chapter. On rare occasions the stenotic bronchus may be relined by squamous epithelium, and even more rare is a complete occlusion of the bronchus by scar tissue. As it appears that the necrosing process begins in the mucosa without evidence of definite tuberculous lesions, it would seem that the process is initiated by stagnation of sloughing material. This probability is supported by the fact that the most extensive necrotic endobronchial tuberculosis which the writer has seen has been in bronchi distal to a stenosis. A necrotic lesion which is limited to a short segment of a bronchus can be caused by a plug of dispersed sloughing debris lodging in a small bronchus. How frequently this occurs is uncertain because of the difficulty of identifying the contained bronchus from morphologic structure. It may well be more frequent than is commonly thought.

From this study it would seem that bronchi are not readily infected with tuberculosis, considering that they serve as drainage canals for all sloughing lesions. Fortunately, necrotic endobronchial tuberculosis is not a common occurrence. If it does occur, then the problem of complete healing closely simulates that of parenchymal cavity formation.

The bacteriologic findings in necrotic endobronchial disease indicate that the tubercle bacilli are present more often and in larger numbers in the material within the bronchi than in the necrotic bronchial wall itself. Even in the necrotic contents of such bronchi, frequently bacilli are most difficult to find. To the writer the persistent discharge of tubercle bacilli in the sputum in association with endobronchial disease indicates a sloughing parenchymal lesion rather than the mere presence of endobronchial lesions.

In trying to evaluate the effect of chemotherapy on bronchial disease in tuberculosis, it must be borne in mind that much of the residual pathology antedated, frequently for a considerable time, the initiation of the chemotherapeutic regimen. There was little evidence of lymphocytic infiltration of the mucosa in the majority of the specimens with filled-in cavities, provided that the chemotherapeutic regimen had been in effect for many months. However, there were enough exceptions to indicate that individual patients varied and also to indicate that the process of liquefaction and sloughing had not been entirely stopped even in patients who had had a year or more of chemotherapy. Mucosal histologic tubercles and giant cells were found infrequently in the bronchial mucosa in patients who had had long periods of chemotherapy. In the specimens which showed necrotic endobronchial disease and which were removed from patients

after prolonged chemotherapy, the lesions closely resembled similar lesions found in specimens removed after either no chemotherapy or a relatively short course of chemotherapy. In specimens removed from patients who had tubercle bacilli in the sputum at the time of surgery and who had had long-term chemotherapy, the bronchi which led from sloughing lesions, either open or filled-in cavities, showed a rather marked lymphocytic infiltration of the mucosa. The presence of stratified squamous epithelium seemed to be related more to the duration of the disease than to any chemotherapeutic effect.

From these remarks it would seem that the most common bronchial lesion, lymphocytic infiltration of the mucosa, with or without congestion and edema, was related more to active sloughing of parenchymal lesions than to any chemotherapeutic effect. Also that there was little evidence to indicate that necrotic endobronchial lesions were significantly affected by chemotherapy.

PLATES XXV–XXXI follow

PLATE XXV

FIG. 74. (× 5) Section through lower lobe bronchus near its origin and the adjacent structures. Note the penetrating ulcerated area to the right. This lesion also involves the pulmonary artery (present in the upper right quadrant) which ruptured through the bronchial ulcer and caused sudden death from massive hemorrhage. Except for the area of ulceration, the bronchus showed a normal structure. At the edges of the ulcer there was a narrow zone which was covered by stratified squamous epithelium. This suggests that the lesion had existed for a long time although there was no clinical indication of the serious situation. It appeared that the lesion was related to a necrotic tuberculous lymph node, for there were other necrotic lymph nodes present in the same general area. This specimen serves to indicate how serious a situation may be induced by the tuberculous disease extending beyond a lymph node and inducing ulceration through the entire bronchial wall. Tubercle bacilli were most difficult to find except in local areas of undigested and unsloughed dead tissue in the wall of the ulcer. In these places there were masses of bacilli. Sputum had always been negative for tubercle bacilli on microscopy but generally yielded a few colonies on culture. No chemotherapy had been given.

FIG. 75. (× 15) This illustrates the most frequent situation present in bronchi which act as drainage tubes for sloughing parenchymal lesions. There are congestion, edema, and extensive lymphocytic infiltration of the mucosa. An occasional giant cell and a small "epithelioid" tubercle are also present. There is a small focal ulceration in the lower left-hand portion of the mucosa. Ulcerations of this type are not at all common. Otherwise the epithelial covering is intact and is normal. No chemotherapy had been given.

FIG. 76. (× 15) A large bronchial branch with numerous "epithelioid" tubercles and giant cells in the mucosa. In some areas these structures are represented by scar tissue and a few scattered giant cells. This degree of tubercle formation in the mucosa is not the usual picture. The epithelial covering is normal and is completely intact. A small amount of mucopurulent exudate lay within the lumen. This bronchus led to a filled-in cavity. No chemotherapy had been given.

FIG. 77. (× 10) A moderately large bronchus which shows an intact normal epithelial lining. On the right side the mucosa is normal, whereas on the opposite side considerable scar tissue is present. At the lower end there are "tubercles" which are considerably fibrosed. The scars are taken to represent completely healed tubercles. To have so much scarring, there probably were as great a number of tubercles as are shown in figure 76 at an earlier date. This patient had had no chemotherapy.

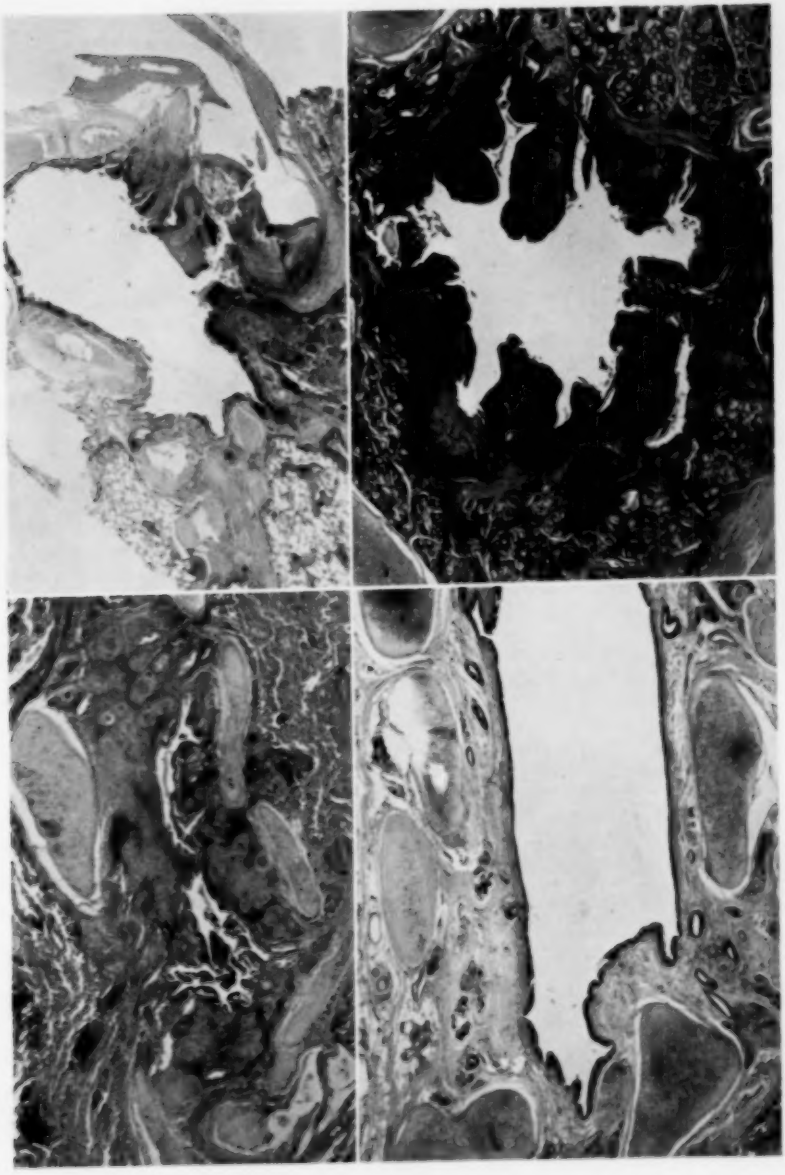


FIG. 74

FIG. 75

FIG. 76

FIG. 77

PLATE XXV

PLATE XXVI

FIG. 78. (× 15) A bronchial branch with a focal mucosal lesion which has undergone necrosis and has eroded the overlying epithelium. The remaining epithelium is intact and is normal. Marked lymphocytic infiltration is present in the major portion of the mucosa. This type of necrosing and ulcerating mucosal lesion is extremely rare, in the writer's experience. It is the only one encountered in the study of resected specimens. This apparently is not the way by which necrotic endobronchial disease usually develops. The writer saw this type of focal ulcerative endobronchial lesions quite often during his study of tuberculosis in cattle. Multiple-drug therapy was given for ten months.

FIG. 79. (× 15) This lesion was 4 mm. across and was spherical in shape. In part, the necrotic area shows the architecture of lung parenchyma. The lesion appears to be well encapsulated. Note the piece of dead cartilage just below the center of the necrotic area. It appears that the lesion is a small area of necrotic pneumonia which includes a small bronchial branch. Without the presence of the cartilage, the identification of a bronchus within the lesion would not be possible. Lesions of this nature probably are much more common in pulmonary tuberculosis than is generally realized. No chemotherapy had been given.

FIG. 80. (× 15) An area of necrotic pneumonia about which the delimiting fibrotic capsule is as yet poorly formed. Note that the connecting bronchus contains necrotic debris which is heavily infiltrated with neutrophils. The portion of bronchus farthest to the right from the necrotic lesion has a normal and intact epithelial lining, and the mucosa is heavily infiltrated with lymphocytes. The remainder of the bronchial mucosa is necrotic, with heavy lymphocytic infiltration beneath the necrotic surface in the lower wall of the bronchus. No tubercles are present. This is taken to represent the early stage of necrotic endobronchial disease. It starts from the inside of the bronchus and apparently is induced by stasis of sloughing material. Note the blue zone in the edge of the necrotic area. This zone is heavily infiltrated with neutrophils. Intact lung framework can be made out, under higher magnification, throughout the necrotic area. No chemotherapy had been given.

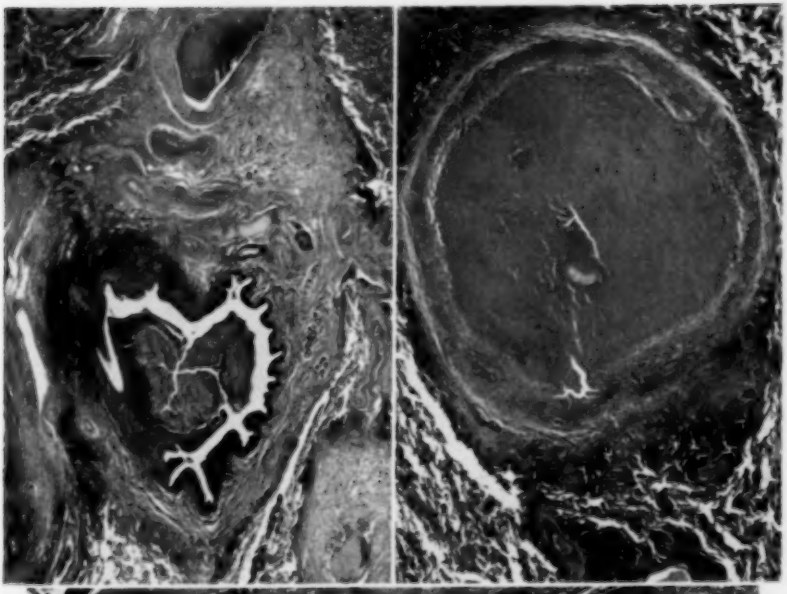


Fig. 78

Fig. 79

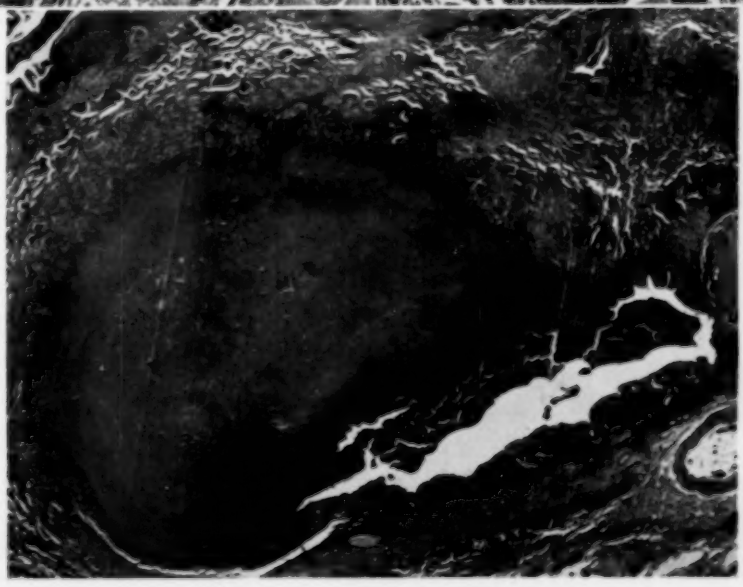


Fig. 80

PLATE XXVI

PLATE XXVII

FIG. 81. (× 10) Complete involvement of a bronchial wall in necrotic endobronchial disease. The bronchus is filled with purulent exudate which is intermingled with necrotic debris. There is a red-staining zone of necrotic fibrous tissue which is in direct continuation with living fibrotic tissue. This structure closely resembles the walls of many tuberculous cavities. Note in the lower left-hand quadrant two pieces of cartilage. One piece was directly involved in the sloughing area, and the other lay just beyond it. As cartilage is present normally in the outer portion of bronchial walls, it is evident that the fibroblastic reaction is well beyond the normal confines of the bronchus. Without the presence of cartilage, this lesion could be assumed to represent a bronchus only from its association with vessels of sizable caliber. Streptomycin was given for ninety days.

FIG. 82. (× 5) The two bronchi are branches of the same bronchus near the hilum. The upper bronchus shows some lymphocytic infiltration of the mucosa and was not related to any tuberculous lesion. The lower bronchus was the one which drained a slitlike open cavity. This latter bronchus showed extensive necrotic endobronchial tuberculosis from its point of origin to its connection with the cavity. Note two pieces of cartilage peripheral to the fibrotic and necrotic zones. Although the lobe had been under thoracoplasty for fifteen years, there was little evidence that the process of necrosis and sloughing had ceased. Several pulmonary hemorrhages occurred five years previous to resection. Combined chemotherapy was begun eighteen months before resection was done. Sputum continued to be positive for acid-fast bacilli on microscopy up to the time of surgery.

FIG. 83. (× 15) Marked bronchial stenosis of a small bronchus brought about in the reparative process of necrotic endobronchial disease. The central portion still is patent and has a necrotic inner lining. Bronchial identification is certain from the piece of cartilage in the upper right-hand quadrant and the associated moderately large blood vessels. The blue areas in the periphery are collections of lymphocytes. This bronchus connected with a cavity which was still patent after one year of combined chemotherapy.

FIG. 84. (× 15) An old stenosed small bronchus which was evidently caused by complete healing of necrotic endobronchial disease. The small open space was filled with mucus and probably represents a small remnant of a mucous gland. The bronchial structure is identified by a small piece of cartilage in the upper right-hand quadrant. This patient had had known advanced pulmonary tuberculosis for several years and had received no chemotherapy up to three months prior to surgery. Lesions of this nature have rarely been found in the study of the resected specimens. However, the illustration serves to indicate that on occasion complete healing of necrotic endobronchial tuberculosis can occur without chemotherapy.

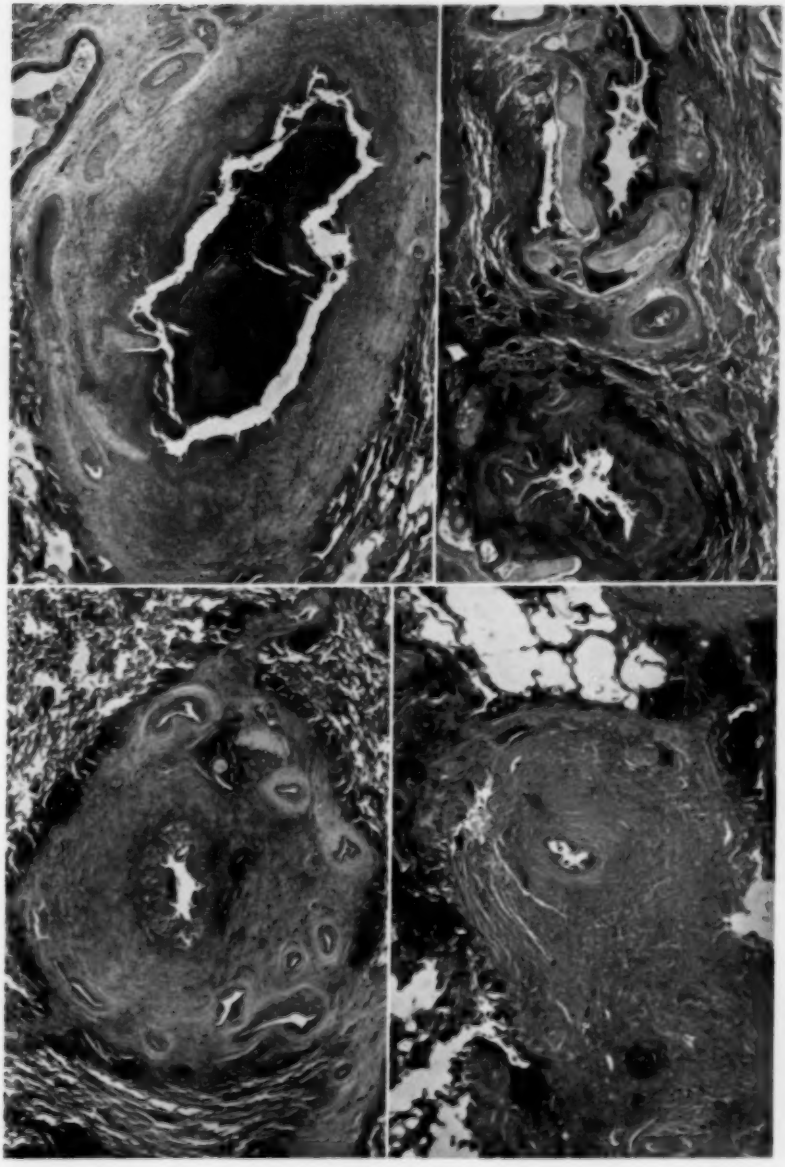


FIG. 81

FIG. 82

FIG. 83

FIG. 84

PLATE XXVII

PLATE XXVIII

FIG. 85. (× 10) Bronchus to filled-in cavity completely closed by scar tissue. Complete occlusion was proved by serial sections. This is the only way to be certain that a small drainage canal is not present within such bronchi. Compare with figure 83. The patent bronchus is present in the lower portion. Here the epithelial lining is intact, and a light sprinkling of lymphocytes and an occasional giant cell are present in the mucosa. The large strand of scar tissue which leads up to the necrotic tissue can be identified as the course of the bronchus by a piece of cartilage to the left near its juncture with the necrotic tissue. Because of the rarity of the condition shown in the illustration, it deserves little consideration in the management of tuberculous patients. A ninety-day course of streptomycin had been given.

FIG. 86. (× 10) On the left of the bronchus with extensive necrotic endobronchial disease, there are three pieces of cartilage peripheral to the fibrotic and necrotic zones. Note that in the left-hand inner portion of the fibrotic zone there is a covering of stratified squamous epithelium. The remainder of the inner surface of the bronchus is necrotic. This suggests that, if the necrotic tissue is sloughed cleanly adjacent to an intact normal epithelial lining, the epithelium which grows out over the cleansed area is of the squamous type—an epithelial metaplasia. The writer has observed this phenomenon on several occasions and is of the opinion that this process is a constant one in the healing of ulcerated areas which involve submucosal tissue. No chemotherapy had been given.

FIG. 87. (× 4) This patient was known to have a stenotic bronchial lesion for several years prior to surgery, and chemotherapy was used only to cover the immediate pre- and postoperative period. Macroscopically, the stenosed bronchus, the lower one in the illustration, showed a small opening through which purulent secretions exuded. It appears that the process of necrosis has been limited largely to the mucosa, and in the reparative process the scar tissue has markedly narrowed the bronchial lumen. In the upper right-hand quadrant the inner surface of the stenosed bronchus is covered by stratified squamous epithelium. In the remaining portion, the inner surface shows a thin superficial zone of necrotic tissue beneath which there is an abundant well-vascularized granulation tissue. Purulent exudate is present in the lumen. This is a segmental bronchus at its point of origin. The bronchus above the stenosed one is another segmental bronchus with only lymphocytic infiltration of the mucosa. The lymph nodes in right center contain some focal scars, residuals of healed tuberculous foci. No chemotherapy had been given.

FIG. 88. (× 4) Section of lung beyond the stenosed bronchus shown in figure 87. The lung parenchyma of the segment was entirely airless with little parenchymal disease. All branches of the stenosed segmental bronchus were somewhat distended with retained secretions, and each of these bronchi had necrotic endobronchial disease to a greater or lesser extent.

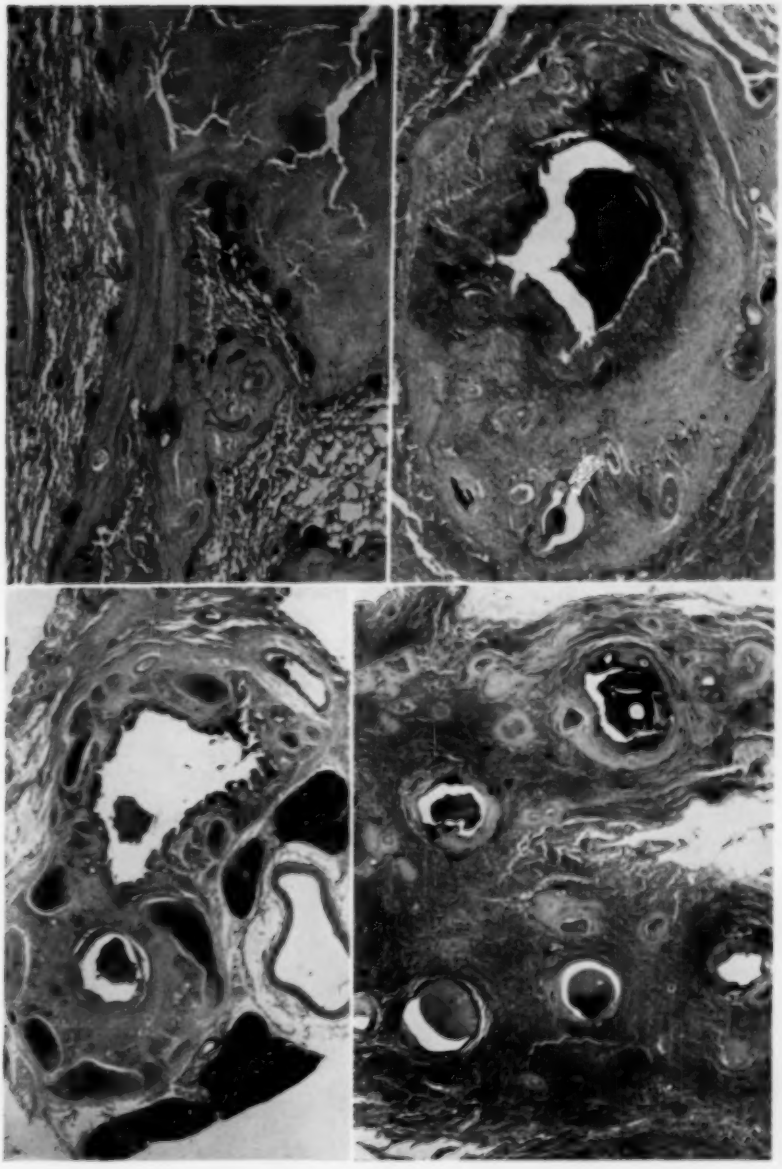


FIG. 85

FIG. 86

FIG. 87

FIG. 88

PLATE XXVIII

PLATE XXIX

FIG. 89. (× 4) Section shows two bronchial branches with marked stenosis (left-hand side of illustration) and others which are filled with necrotic debris without any evidence of healing. Known tuberculosis dates back eighteen years, controlled on one side by pneumothorax of three years' duration. Fourteen years later progressive disease developed in the upper lobe of the opposite lung. Streptomycin-PAS therapy was given for fourteen months prior to surgery. Sputum was negative for tubercle bacilli for four months prior to surgery. Bronchoscopic examination showed no evidence of bronchial stenosis four months prior to surgery. All of the endobronchial involvement was found in branches beyond the hilar region. The lobar bronchus at point of resection showed only lymphocytic infiltration of the mucosa.

FIG. 90. (× 4) Marked distension of bronchi beyond a stenosis of a small bronchus well out in the lung parenchyma. The distended bronchi extended to just beneath the pleura and were filled with a mucopurulent exudate which was more mucoid than purulent. There are focal areas of necrotic ulceration. Otherwise there is little other than a light sprinkling of lymphocytes in the mucosa. The writer has observed several lesions of this type in the resected specimens. Multiple-drug therapy was given for six months.

FIG. 91. (× 15) The two sections are from the specimen mentioned in the text in which a bronchus had been dissected free during surgery. The larger section is from the beadlike enlargement of the bronchus. This lesion was spherical in shape and measured 4 mm. in diameter. Without knowing the relationships, one could hardly establish this lesion as being a bronchial one with involvement of the surrounding lung parenchyma. The slitlike central opening permitted easy passage of a thin wire probe. It also seems probable that air could also pass through this lesion. The bluish areas in the necrotic area show, on higher magnification, a large amount of nuclear "dust," and an occasional neutrophil was identifiable. Should a necrotic lesion of this type liquefy and should tubercle bacilli be present, it can readily be seen how further endobronchial dissemination could ensue. In the opinion of the writer, lesions of this nature may be much more common than is now thought.

The smaller section is the bronchus within 1 mm. of the necrotic lesion. The epithelial lining is intact. The mucosa is considerably infiltrated with lymphocytes, and an occasional giant cell and small "tubercle" are present. Chemotherapy was given only to cover surgery.

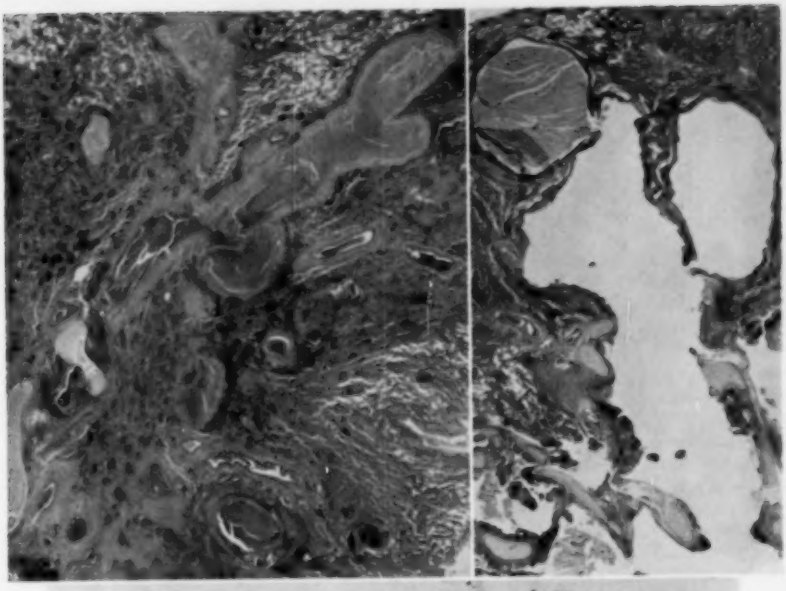


FIG. 89

FIG. 90

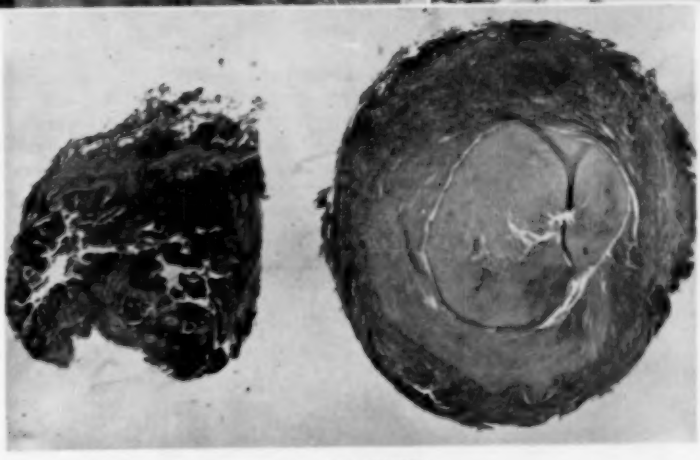


FIG. 91

PLATE XXIX

PLATE XXX

FIG. 92. (× 5) Section from specimen, mentioned in text, which was serially sectioned. This is at a level of the largest portion of the necrotic lesion. There is no bronchial communication, and the lesion is completely encapsulated. The bluish color at the periphery is due to considerable accumulation of lymphocytes. An intact dead lung framework is identifiable on higher magnification. The smaller lesions in the surrounding tissue are endobronchial disseminations. Multiple-drug therapy was given for eight months.

FIG. 93. (× 15). Same patient as above. The slitlike bronchial connection from the left is lined with stratified squamous epithelium. This epithelial covering continues for an appreciable distance over the clean inner surface. The bronchial opening was present in only three consecutive sections. The epithelium covered scarring tissue that was considerably infiltrated with lymphocytes. Apparently this bronchus had been completely necrosed. With clean sloughing, the bronchus became relined with epithelium rather than obliterated by scar. The bluish color of the necrotic tissue to the right is due to infiltration with neutrophils.

FIG. 94. (× 15). Same patient as above. Illustration shows second bronchial communication. This one extended through six consecutive sections. The bronchus is normal, except for lymphocytic infiltration of the mucosa, up to its juncture with the necrotic lesion. At this point the epithelium changes to squamous type. An appreciable area of the cleansed inner surface of the fibrotic "capsule" is covered with squamous epithelium. Note that the epithelial covering on the right continues until it abuts upon necrotic tissue. Blue color in necrotic tissue in upper left quadrant is due to heavy infiltration with neutrophils.

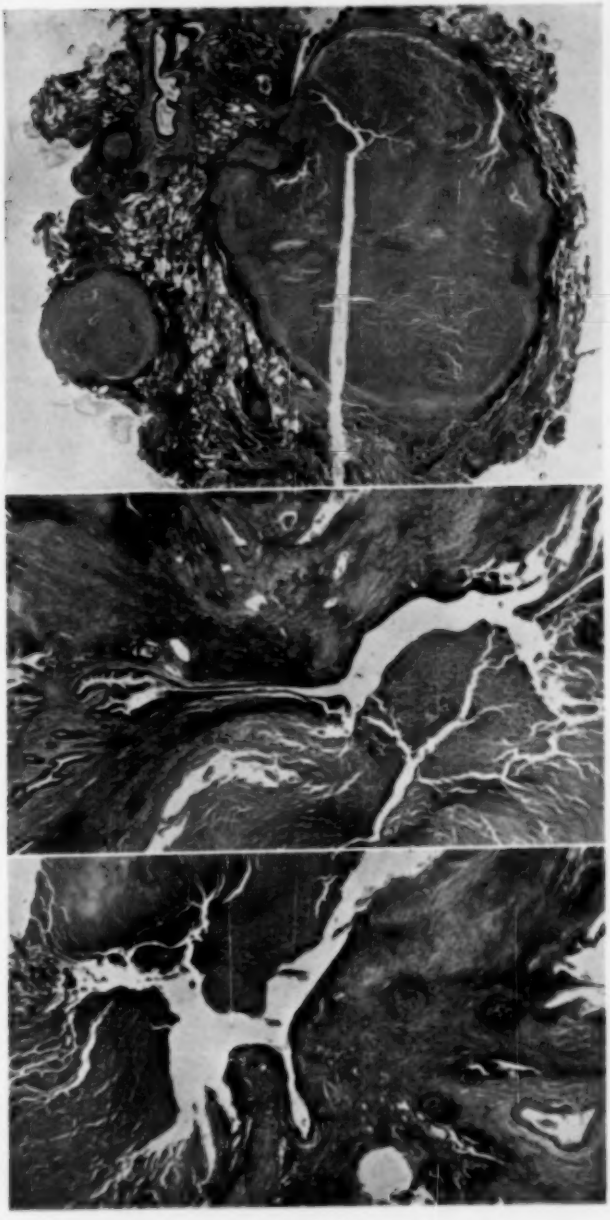


FIG. 92

FIG. 93

FIG. 94

PLATE XXX

PLATE XXXI

FIG. 95. (× 4) Bronchial connection with sloughing parenchymal necrotic lesion. The bronchus contains purulent exudate. In the illustration the bronchus is in a state of sloughing. Near the parenchymal lesion in the upper wall of the bronchus, note the piece of cartilage which is also being sloughed. There is no epithelial lining of the bronchus. The parenchymal lesion is surrounded by a fibrotic "capsule" which continues down along the bronchus. In part, the necrotic area has lost its lung structure; and, in part, this structure is intact. The bluish areas in the necrotic area are due to heavy infiltration with neutrophils. Note the separation between the dead and living tissue in some portions and the lack of it in others. This patient had been receiving streptomycin-PAS therapy for seven months.

FIG. 96. (× 15) Section shows a covering of stratified squamous epithelium of areas of inner surface of a filled-in cavity near the junction of bronchus and cavity. This patient had been known to have pulmonary tuberculosis for eight years. After three years of hospital treatment, he was discharged as having arrested tuberculosis. He worked for two years; then had a relapse. The patient had further bed-rest therapy for one year and thoracoplasty four years prior to resection. He received chemotherapy for two months prior to surgery. The resected lobe showed a large necrotic mass, only a portion of which had liquefied and sloughed to permit cavity formation. The outgrowth of epithelium which, in the writer's experience, is always of the stratified squamous type would appear to be related to the age of the disease rather than to the effect of chemotherapy.

FIG. 95

FIG. 96

PLATE XXXI

CHAPTER VIII

TUBERCULOSIS AND BRONCHIECTASIS

There is considerable literature which implicates bronchial damage caused by the infection as the etiologic factor for bronchiectasis in pulmonary tuberculosis. In large part, this literature deals with bronchographic findings and, in the writer's opinion, there is an insufficient documentation of the subject by pathologic facts. In the present discussion, the microscopic findings obtained from a study of nontuberculous bronchiectatic specimens will be presented first, to be followed by a similar study of tuberculous specimens in which bronchiectasis also was found.

Among the specimens resected from 295 tuberculous patients, bronchiectasis and tuberculosis were found to coexist in 26 patients. A clinical diagnosis of bronchiectasis had been made in only 5 of these 26 patients. During the same period, eighteen specimens from nontuberculous patients were examined. These all showed bronchiectasis without evidence of progressive tuberculosis. In 5 of these cases a clinical diagnosis of chronic lung abscess had been made, and in each instance the pathologic process was one of cystic bronchiectasis. Consideration also will be given to 5 additional patients. One was a forty-five-year-old Negro, from whom a lobe with a chronic lung abscess was resected. The second was a sixty-one-year-old white male, from whom a lung was removed because a tumor mass largely obstructed the lumen of the main bronchus. A third case was that of a thirty-one-year-old white female with a clinical history dating back to the age of fifteen whose pulmonary condition was diagnosed as bronchiectasis. The fourth specimen was a right lung which was removed from a ten-year-old boy. In this case the pulmonary complaints dated back to a tonsillectomy which was performed two years previously. The fifth specimen was a right upper lobe removed from a twenty-year-old white tuberculous male.

Thus, the data and discussion in this chapter will be based upon observations on specimens removed from 49 patients, of whom 27 underwent surgery for pulmonary tuberculosis and 22 for nontuberculous pulmonary disease.

The writer is aware of the considerable volume of literature on the subject of bronchiectasis. As the data and discussion in this monograph deal with his own study of the problem of tuberculosis, however, it would seem to be out of place to attempt an adequate review of the literature on bronchiectasis. Excellent reviews of this subject are already recorded. Briefly, one may state that there are four hypotheses relative to the pathogenesis of bronchiectasis.

First, the process is considered to be initiated by an episode of necrotizing bronchitis, usually in young children as a complication of measles or whooping cough. Second, the condition is induced by an obstruction within or without bronchi or

bronchioles, with a suppurative bronchial disease either proximal or distal to the obstruction. The third concept considers that the large bronchi are caused by traction exerted by parenchymal scars. The fourth hypothesis considers the process to be related to a malformation of the pulmonary structure on a congenital basis.

The writer is not aware that typical bronchiectasis has been observed in the lungs of newborn infants.

In the study of necropsy material reported in a previous chapter, the many variations in lung structure which were found in the size of pulmonary lobes and in the status of fissures were listed. Thoracic surgeons are even more aware than pathologists that considerable variation occurs in the vascular pattern of lungs. Inasmuch as the writer sought to detect minute tuberculous lesions by examining fresh pulmonary tissues with ungloved fingers, he has become increasingly aware of subtle variations in lung structure.

There is an appreciable variation in the sturdiness of structure of the lung parenchyma. This seems to be related to the amount of connective tissue which is present. Also, there is an appreciable difference in the sturdiness of structure of the bronchial tree. This is related largely to the amount of connective tissue and of cartilage. In some lungs, macroscopically detectable bits of cartilage are to be found at the bifurcation of minute bronchi which lie near the pleura, whereas such cartilage is absent from other lungs. The amount of cartilage in the larger bronchi also varies considerably. In some large bronchi the amount of cartilage is so small that the bronchi collapse easily, whereas in other lungs smaller bronchi contain a sufficient amount of cartilage to prevent collapse of the structure.

It is well recognized from bronchoscopic examinations that, in some instances, large bronchial branches may collapse on expiration. This condition has been considered to be due to chondromalacia and on occasion has been ascribed to an infectious process. It seems probable that it is related primarily to a natural developmental structure of such bronchi rather than to any infectious process.

There also is a considerable variation in the diameters of bronchi. This variation poses a question with regard to the upper limit of size beyond which bronchi are to be considered ectatic. This pertains particularly to the condition of cylindrical bronchiectasis. In bronchographic studies the variation in size of normal bronchi also presents a problem with regard to the interpretation of the bronchial pattern.

In this study of bronchiectasis, it was thought pertinent to study the prenatal development of the lungs in order to understand the changes in lung structure which occur during post-natal growth. The lung develops prenatally as a glandular organ with larger and smaller epithelial-lined tubules. At approximately the fifth month of fetal life, these tubules (Plate XXXII, figure 97) are present throughout the organ and are separated by small vessels and a rather large amount of young connective tissue. The lobes are well demarcated by this time, but the interlobular septa and the pleura are inconspicuous. At seven months, the pleura, vascular pattern, and interlobular septae are well developed. The larger tubules which are destined to become the main bronchial branches are much less numerous than the small tubules (Plate XXXII, figure 98) which

extend out to the pleura. Proportionally, less connective tissue and more blood capillaries are observed between the tubules than at the fifth month of fetal life.

In the group of fetal lungs examined, one was from an infant who was born at seven months and who lived only twenty-four hours. In this specimen the majority of small tubules (Plate XXXII, figure 99) were considerably expanded with air, and it was difficult to identify epithelial cells, either free within the lumen or lining the wall, in the expanded tubules. In another case the infant was born at seven and one-half months and lived for thirteen days. In this specimen practically every small tubule (Plate XXXII, figure 100) was air-containing, and the bronchial pattern had become an inconspicuous part of the organ. Many of the tubules which had become alveoli were so distended with air that the lung suggested an emphysematous condition. Now the intertubular connective tissue, although greater than in an adult lung, was much less apparent than in the seven-month specimen from a stillborn infant. It was extremely difficult to identify epithelial cells, either free in the alveolar lumina or on the alveolar walls.

From these observations it would appear that shortly after birth the small epithelial-lined tubules do become alveoli, and the major portion of the lung becomes parenchyma from a distension and growth of the prenatal tubules. The fate of the epithelial lining of the tubules, whether the cells are sloughed or whether they become greatly flattened out as a covering of the distended tubules, does not concern us here other than that alveoli originate from epithelial-lined tubules. Undoubtedly, with the growth of the lung parenchyma the bronchi, vessels, and connective tissue grow apace to form the normal lung structure of the adult. In the study of bronchiectasis it is necessary to keep in mind the effect that an imbalance in the development of the different components of normal lung might have upon the morphology of a lobule, a segment, a lobe, or even of an entire lung. That aberrations of development do occur prenatally is shown by the occasional finding in young infants of bronchiogenic cysts and of cystic disease of the lung. It also seems possible that further aberrations of development of the lung may occur during the post-natal growth to maturity. Because of the known variations in the development of fissures and in the size of pulmonary lobes, post-natal aberrations in the intrapulmonary development should receive as serious consideration as the occurrence of infections in a study of the pathogenesis of bronchiectasis.

BRONCHIECTASIS WITHOUT TUBERCULOSIS

Before a discussion of the possible relationship between bronchiectasis and tuberculous infection is undertaken, it would seem best to consider the morphologic features of bronchiectasis in persons who do not have progressive tuberculous disease. This discussion will be limited to the study of specimens removed from 22 patients who revealed no clinical evidence of a tuberculous infection and in whose resected specimens no evidence of progressive tuberculous disease was found. In 4 adult patients, a minute old fibrotic or fibrocalcific tuberculous

pulmonary lesion was found in a portion of the specimen which was not directly associated with the bronchiectatic process. At least one lobe of lung was resected in each case, and each pulmonary lobe occurred at least once in the series. Three of the patients were less than ten years of age, 2 were between the ages of ten and thirty, and the remaining 17 patients ranged in age from thirty-one to sixty-six years. The specimens came from both males and females.

The first significant macroscopic feature of the twenty specimens in which a clinical diagnosis of either bronchiectasis or chronic lung abscess had been made was the absence of any stenosis or other evidence of obstruction to the bronchi at the point of resection. In all but one specimen, the segmental bronchi also appeared normal at the point of origin. In one specimen, a left lower lobe from a sixty-two-year-old white male, all segmental bronchi except the one to the anterior basal segment presented a round lumen of normal size and appearance. The bronchus to the anterior basal segment presented a slitlike opening which was ulcerated. The slitlike opening was caused by the presence of a long thick piece of cartilage along one side which prevented the bronchus from assuming a round shape, such as was present in all other segmental bronchi. The major branches of this segmental bronchus contained mucopurulent secretions and showed marked cellular infiltration of the mucosa with focal areas of ulceration. All of the other bronchi in the lobe showed no evidence of inflammatory reaction in their mucosae and contained no exudate.

Further study of this lower lobe showed that the bronchial tree of the superior segment was of normal proportions, whereas the segmental bronchi to all basal segments were unusually sturdy in structure and larger than normal, even adjacent to the diaphragmatic pleura. Sections taken within one-half centimeter of the diaphragmatic pleura showed bronchial branches which were of greater dimensions than the segmental bronchi at point of origin. These large bronchi (Plate XXXIII, figure 101), regardless of the presence or absence of evidence of infection, showed an unusual amount of cartilage which was associated with fat tissue and a paucity of smooth muscle. In addition there were sizable mucous glands, normal columnar ciliated epithelial linings, and larger and more numerous blood vessels than one would anticipate in association with bronchi so close to the diaphragmatic pleura. This lobe also contained abnormally large bronchial branches which had thin walls without cartilage, irregular distributions of smooth muscle, and normal columnar ciliated epithelial linings.

The lung parenchyma in the lobe was abundant, of delicate structure, and somewhat emphysematous. An occasional small parenchymal scar was present. A somewhat similar condition was found in the inferior division of the lingula of the upper lobe. In this case it would hardly seem possible to ascribe the condition as a sequel to a suppurative process in the bronchi.

Another common feature of the abnormally large bronchi was that they seldom were of uniform diameter throughout. In some instances a bronchus was of fairly normal caliber for a distance and then ballooned out to a cystic structure with a diameter of one centimeter or more. Such bronchi showed no evidence of compression from without or of stenosis from within, and they had normal columnar ciliated epithelium.

This situation was well illustrated by a left lower lobe which was removed from a fifty-six-year-old white housewife. This patient had a history of "chest trouble" dating back to childhood. For years she raised considerable quantities of nonfoul mucoid secretions which later became mucopurulent, and during the last ten years the sputum had a foul odor. Again the bronchi were of normal proportions in the hilar portion of the lobe. The lobe contained much less normal parenchyma than the one commented upon above.

On section of the lobe, numerous cystic areas (Plate XXXIII, figure 102) which ranged up to 4 centimeters in diameter were observed. Most of these were full of a mucopurulent exudate, but a few were empty and collapsed. These cysts were a ballooning-out of bronchi which, proximal to the cyst, were of normal dimensions. There was no evidence of bronchial stricture proximal to the cysts, and the epithelial linings were of the normal columnar ciliated type. The cysts, whether infected or not, all had delicate walls in which there was no evidence of cartilage, little evidence of smooth muscle, and linings of ciliated columnar epithelium. The infected cysts showed areas of ulceration and, in some areas, the ulcerated foci had healed to some degree by the covering of clean granulation tissue by stratified squamous epithelium. In this same general region there were several abnormally large noncystic bronchi which were filled with mucopurulent exudate. The epithelial linings of these bronchi were normal, except for focal ulcerations, and the bronchial walls contained a variable amount, from none to considerable, of smooth muscle and cartilage. In some there were moderately large mucous glands. An occasional empty cystic structure showed an epithelial lining which was suggestive of the lining of the esophagus. There was no evidence of cellular inflammation or of scar tissue beneath the epithelial lining in two cysts of this type.

Macroscopically, there were a few small firm grayish areas which were considered to be foci of lobular pneumonia. On microscopic examination, these areas contained numerous small tubular structures which were lined by cuboidal epithelium and a few large emphysematous alveoli. These areas were more suggestive of lobules of fetal lung which had failed to develop fully than of an organizing lobular pneumonia. In association with the bronchiectatic process, there were rather broad bands of connective tissue in which vessels were numerous. These areas were not of the structure of scar tissue. Although rather large areas of lung parenchyma were present, they seemed to be rather poorly developed except in the superior segment of the lobe. This was quite in contrast to the condition of the parenchyma noted in the previous case.

In a few of the specimens, considerable tortuosity of the bronchi was found, which superficially suggested the presence of strictures. This condition was due to a redundancy of the mucosa, which caused it to project into the lumen of the bronchus either as a papillomatous or as a shelf-like structure. Microscopic examination of such bronchi showed a normal ciliated epithelial lining and no evidence of scar formation in the bronchial walls. In these specimens it would seem that too much bronchus was present for the space available.

This condition was well illustrated by a right middle lobe which was removed from a thirty-one-year-old white female whose clinical history dated back to the

age of puberty. The lobe was very much smaller than normal, firm, and contained little air. For a considerable part the pleura appeared thickened and of a pinkish-gray color. However, there were only a few, focal, delicate pleural adhesions. The bronchi at point of resection were within normal limit, and no evidence of stricture or obstruction was observed. On section, the lobe (Plate XXXIV, figure 103) was found to be occupied to a large extent by abnormally large, tortuous bronchi which extended to the pleural surface. The bronchi contained only small amounts of mucus. The vascular patterns were unusually prominent. There appeared to be little lung parenchyma.

On microscopic study (Plate XXXIV, figure 104) the pleura, for the most part, presented a normal appearance, but beneath the pleura was a zone in which there was a poorly developed lung parenchyma. The tissue in this zone did not present the morphologic appearance of an organized pneumonia. The lung parenchyma throughout the specimen presented a similar appearance and was rather scant in amount.

The bronchi varied considerably in structure in different areas. Some showed an overabundance of cartilage for a distance, and then there would be a rather large area without any cartilage. The same situation was found in relation to smooth muscle. Some large thin-walled bronchial branches were entirely devoid of smooth muscle, whereas others contained an overabundance in some and none in other areas. All bronchi were lined with normal columnar ciliated epithelium. Some of the bronchi showed marked lymphocytic infiltration of the mucosa and focal areas of ulceration. Others were devoid of both cellular inflammatory reaction and ulceration. Large and numerous blood vessels were present. To the writer, it seems rather difficult to attribute all of the abnormal conditions found in this specimen to the sequelae of infection.

A specimen which was removed from a sixty-four-year-old white male was of particular interest because of the condition of the right middle lobe. The lower lobe contained an abundant delicately constructed parenchyma which was somewhat emphysematous. The bronchiectatic portion of the basal segments consisted of abnormally large thin-walled bronchi (Plate XXXIV, figure 105), some of which were cystic, with diameters of two centimeters. These bronchi at the time of operation contained only slight amounts of clear mucus. Microscopic study showed little or no cartilage, a very irregular distribution of smooth muscle, little cellular infiltration of the mucosa, and a normal ciliated epithelial lining. One of the large cystic bronchi showed a small local ulceration and also a small area of scar tissue which was covered by stratified squamous epithelium. This was the only evidence which could be related directly to an infectious process. There were numerous bands of connective tissue in association with the bronchi. Morphologically, this tissue did not resemble scar tissue, and in some areas moderately large vessels, nerve fibers, and bundles of smooth muscle were found.

The middle lobe was perfect in shape, but it was airless and was only approximately the size of a Brazil nut. The bronchus to the lobe was small but fully patent. It extended into the lobe less than one centimeter. Section of the lobe

(Plate XXXIV, figure 106) showed an entire absence of bronchial and alveolar structures. It was composed of connective tissue and an abundant vascular supply. This lobe would seem to represent a congenital anomaly with failure to develop a normal lung structure, although the bronchus to the lobe and an abundant vascular supply were present. It was of particular interest because of the presence of bronchiectasis in the lower lobe.

In two specimens bronchiogenic cysts were observed in bronchiectatic lobes. The cysts were distended with clear mucus to such an extent that the ciliated epithelial linings were markedly flattened and no open bronchial connection was found.

In two middle lobe specimens which were removed from adults in their late twenties, the bronchiectatic process was markedly limited. In one, a medial segment only was involved; in the other, only the inferior portions (Plate XXXV, figure 107) of both segments were ectatic. Since both patients had a clinical history of raising sputum which at times was bloody and as bronchographic studies in both had revealed a bronchiectatic condition, it is of interest that the process was so localized.

Two lobes removed on the clinical diagnosis of chronic lung abscess will be discussed briefly. They both proved on pathologic examination to demonstrate infected cystic bronchiectasis. A left upper lobe was removed from a white male, aged fifty-six years. A satisfactory clinical history was unobtainable because of language difficulties. The principal interest in this specimen was the presence of two separate cystic areas, each of which measured three centimeters in diameter and both of which contained considerable mucopurulent secretions. One of these cysts showed a nonulcerated condition, with a complete lining of ciliated columnar epithelium. The other cyst (Plate XXXV, figure 108) was involved with such extensive ulceration that ciliated epithelium remained in only one part. There was an extensive outgrowth of stratified epithelium over the cleansed portion of the ulcerated surface. This situation has been observed on other occasions in bronchiectasis, and it would seem that ulcerated lesions in ectatic bronchi heal in a manner similar to ulcerations of normal bronchi, namely, by a covering of metaplastic epithelium.

Other abnormalities were also present in the tissue about the cysts. One of these was the presence near the pleura of a bronchus (Plate XXXV, figure 109) with a small lumen, sizable mucous glands, a normal ciliated epithelial lining, a large semicircular piece of cartilage, and no evidence of cellular infiltration in the mucosa. Also in association with this bronchus there were moderately large vessels.

The second specimen was a right lower lobe which was removed from a white male of thirty-five years. This man had been free of respiratory complaints until approximately six months prior to surgery, at which time he developed pneumonia. The cystic bronchiectasis in this case closely resembled that found in the previous case except that there was no evidence of healing of extensive ulceration in one of the cysts. The basilar portion of the lobe was of delicate texture and, macroscopically, seemed to be markedly emphysematous, with bullae

present. Microscopic study, however, showed numerous thin-walled cysts (Plate XXXV, figure 110) which were lined with either ciliated columnar or cuboidal epithelium. In this portion of the lobe there were a few small focal areas of lobular pneumonia and a few small irregular parenchymal scars which probably represented organized areas of lobular pneumonia. It would seem that in this case the bronchiectatic condition could be related to a marked aberration in development rather than to the fairly recent infection.

The writer has had little opportunity to study surgically removed chronic lung abscesses. One specimen of this nature was studied. It was a markedly distorted right upper lobe which was removed from a forty-five-year-old male Negro. Seven years previous to resection this man had been hospitalized for five months for a putrid lung abscess. A return of the same symptoms occurred approximately three months prior to resection.

The resected lobe was markedly roughened by dense pleural adhesions and was much smaller and more firm than normal. There was a four-centimeter cavity in the lobe and four separate bronchial openings were present close to the hilar region. The inner surface of the cavity was granular and of a reddish-gray color in considerable areas and was smooth and of a grayish color in some portions, especially in the part adjacent to the bronchial openings.

Microscopic study showed a thick zone of scar tissue surrounding the cavity. The bronchi connecting with the cavity showed a normal columnar ciliated epithelium up to the point of junction, and from this point there was an outgrowth of stratified squamous epithelium (Plate XXXVI, figure 111) over rather large areas. The remainder of the inner surface of the cavity was composed of granulation tissue which was infiltrated with a variable mixture of leukocytes. No evidence of a ciliated columnar epithelial lining was found. In the remainder of the lobe, a considerable amount of parenchymal scarring was found. The bronchial and vascular pattern was consistent with that commonly found in shrunken and distorted infected lobes. No evidence of bronchiectasis was found. The pleura was markedly thickened by dense pleural adhesions.

The condition found in the cavity-bearing area is consistent with the slow repair which one would expect to find in an open space which had persisted long after the sloughing of a considerable area of suppurative pneumonia. A similar condition is sometimes found in a tuberculous cavity of long standing except that the process of necrosis is much in evidence. The presence of stratified squamous, rather than columnar ciliated, epithelium as a partial lining of these cavities indicates clearly that they are not cystic bronchi. Although considerable ulceration may occur in cystic bronchi and a covering of the once ulcerated surface by stratified squamous epithelium does occur, the writer has not seen a cystic bronchus which did not show considerable areas of columnar ciliated epithelial lining.

An instance of bronchiectasis which was distal to an obstruction of the bronchus was found in the right lung of a sixty-two-year-old white male. This patient had had a chronic cough for several years. Approximately eight months prior to resection, the cough became worse and considerable sputum was raised. From

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An instance of bronchiectasis which was distal to an obstruction of the bronchus was found in the right lung of a sixty-two-year-old white male. This patient had had a chronic cough for several years. Approximately eight months prior to resection, the cough became worse and considerable sputum was raised. From

that time on several episodes of pneumonia occurred which were accompanied by fever, chills, night sweats, and loss of weight. Bronchoscopic examination showed a tumor mass which protruded from the upper lobe bronchus and acted as a ball-valve mechanism in the right main bronchus.

Examination of the specimen showed a mushroom-shaped tumor which arose from the wall of the upper lobe bronchus proximal to a division into segmental bronchi. The stem of the tumor was large enough so that only a slitlike space was present between the bronchial wall and the tumor growth, and the larger distal portion largely filled the lumen of the main bronchus. There were no enlarged firm hilar lymph nodes. As the tumor was lifted out of the main bronchus, considerable mucopurulent exudate welled up from the upper lobe, and frothy mucoid secretions from the lower and middle lobe bronchi were noted. Numerous widely scattered firm nodular areas were palpated in the upper lobe, whereas the lower and middle lobes were of normal consistency.

On section, the lower and middle lobes were not unusual. Throughout the upper lobe there were scattered firm areas, some of which were of a reddish color; others were of a reddish-gray color, and some were grayish-white in color. All of the bronchial branches near the hilar region were filled with mucopurulent exudate. In the superior portion of the lobe the bronchial branches were largely empty, whereas in the inferior portion of the anterior and posterior segments the bronchi were filled with exudate. The bronchi in the anterior segment did not appear to be of unusual size. In the lower portion of the posterior segment, however, there were bronchi which were considerably ballooned out with exudate.

Microscopic study showed that the tumor mass was a leiomyosarcoma which arose from, but did not invade, the bronchial wall to any extent. Sections from the lower and middle lobes showed a few small foci of lobular pneumonia. Otherwise these lobes presented a normal appearance.

Sections from various portions of the upper lobe showed numerous areas of lobular pneumonia. Some lesions seemed to be of recent origin, and others were the scars of organized pneumonia. The bronchi which contained mucopurulent exudate all showed some inflammatory cellular reaction in the mucosa, but otherwise the bronchial structures were normal, except for several bronchial branches (Plate XXXVI, figure 112) in the inferior portion of the posterior segment. These latter bronchi were considerably larger than the remaining branches, and they extended out nearly to the pleura. The bronchial walls were thin, contained no cartilage, and showed an irregular distribution of smooth muscle. There was a normal ciliated epithelial lining. A few small focal ulcerations were found. Otherwise there was no evidence of a destruction of the bronchial walls.

From the variety of morphologic features, it seemed evident that there had been successive episodes of lobular pneumonia. However, there was no evidence of a destruction of lung parenchyma other than a functional loss from patches of organized lobular pneumonia; neither was there evidence of a destructive process in the bronchi other than a few focal ulcerations. This condition is all the more remarkable for the reason that for perhaps six months an ideal situation existed for the development of a suppurative pneumonic process beyond an

intrabronchial obstruction. The only evidence of abnormally large bronchi, hence of bronchiectasis, was limited to some bronchial branches in the inferior portion of the posterior segment. It seems probable that these abnormal bronchi existed prior to the obstructive process which preceded the infection of the lung. Because of the condition found in this specimen, it would seem to be discreet not to attribute the presence of bronchiectasis in lungs after an episode of pneumonia as a sequel to the infection. Perhaps in these cases bronchiectasis was present prior to the infection.

The last two specimens to be discussed came from two white boys, one aged seven and the other aged nine. The seven-year-old had a history of cough and the raising of sputum, and bronchograms showed an extensive bronchiectasis of the left lower lobe. At operation the lobe was found to be abnormally small, and no pleural adhesions were present. Grossly, the lobe was perfectly formed, was firmer than was normal, and contained little air. The pleura was normal. The bronchus to the lobe was found to be fully patent and of good proportions, and the segmental bronchi were normal at the point of origin. On section the bronchial branches were both more numerous and larger than was normal from the apex to the diaphragmatic pleura. As a consequence, there was much less parenchyma than normal.

Microscopic study of sections from various levels of the lobe revealed an almost identical morphologic picture throughout. Although the bronchi (Plate XXXVI, figure 113) were of good size, little cartilage was present in any and none in the majority. Many of the bronchi were surrounded by a broad band of connective tissue, and in some there were small lymph nodes with germinal centers within the connective tissue. In some of the bronchi the surrounding connective tissue was scant. Smooth muscle was scant in most bronchi but was abundant in a few. The epithelial lining of all bronchi was of the normal columnar ciliated type. In only a few of the bronchi was there a collection of mucopurulent exudate, and in these bronchi a moderate to mild degree of lymphocytic infiltration was present. Moderately large blood vessels were abundant. In considerable areas the lung parenchyma contained no alveoli, and in areas in which alveoli were present they were of small size. There was considerably more lymphoid tissue than one would expect to find in a normal lung. These features suggest a marked aberration in the development of the lobe with too great a bronchial system and far too little lung parenchyma.

In marked contrast to this morphologic picture was the right lung which was removed from the nine-year-old boy. In this case the respiratory symptoms dated back for two years, at which time a tonsillectomy was performed. The operation was followed by a rather stormy febrile illness which resembled pneumonia. Bronchoscopic examination a short time before surgery showed a small bronchus which had an inflamed mucosa and which was interpreted as the right upper lobe bronchus. A large bronchus, going to the right, was thought to represent the right lower lobe bronchus. Bronchograms of the right chest showed that the small bronchus was patent for only a short distance. The bronchial tree in the lower right chest filled well and gave a normal pattern for a lower lobe. At

operation the small bronchus was found to be the main bronchus to the right lung. The mediastinum was markedly deflected to the right, and the major portion of the right chest was occupied by the left lower lobe. At operation the right lung was pink in color and was aerated. It would not deflate or inflate to any degree.

The lung was small but perfectly shaped. There were no fissure lines. However, on section it was observed that three lobes were almost wholly separated from each other by a zone of connective tissue. The pleura was of normal thickness. The upper and lower lobes were air-containing and gave the appearance of emphysema. The middle lobe and a small portion of the other lobes in the hilar region were airless. The main bronchus at the point of resection was no larger than one would expect a segmental bronchus to be. The pulmonary artery and vein were of equally small size. The largest vessel found was a vein which passed from the hilar region downward and left the lung structure approximately three-fourths of the way down the mesial surface of the lower lobe. This vessel at operation was found to pass on down through the diaphragm.

Microscopic study (Plate XXXVI, figure 114) was made of several different portions of the lung. The predominant morphologic picture in the upper and lower lobes was an abundance of delicate well-aerated parenchyma and an inconspicuous bronchial system that was composed, in large part, of unusually small bronchi. Two bronchial branches with large lumina and thin walls were in one portion of the lower lobe. There were a few small areas in these lobes from which alveoli were absent. Also patches of connective tissue were noted in which bundles of smooth muscle were numerous. The middle lobe, although airless, showed numerous alveoli in part and no alveolar structures in some areas. This also applied to the airless portions of the upper and lower lobes in the hilar region. There was no evidence of cellular inflammatory reaction in any of the sections, and little lymphoid tissue was present.

In contrast to the previous specimen, this one revealed a fairly well-developed parenchyma of the lung and an underdeveloped bronchial tree. It would seem that the bronchial branches admitted sufficient air to keep the major portion of the lung inflated, but that the ingress and egress of air was so slow that ready expansion and collapse of the lung were impossible. However, the bronchial system was of sufficient caliber in the middle lobe and in a small part of the hilar portions of the other lobes to permit complete collapse of the parenchyma in those areas. The two large thin-walled bronchi observed in the lower lobe could be regarded as relatively ectatic when compared with the remainder of the bronchial system. These morphologic features, together with the anomalous vascular system and other aberrations in structure, would seem to point to a congenital factor in lung development.

BRONCHIECTASIS AND TUBERCULOSIS

In the previous section the bronchial lesions which are related directly to tuberculous infection have been discussed. The morphologic variations found in bronchiectatic specimens in which there is no tuberculosis have been presented.

This information will facilitate an analysis of specimens in which both tuberculosis and bronchiectasis are present. The group of cases which will form the basis for this study consists of twenty-seven resected specimens.

The normal bronchial pattern in tuberculous lungs may become distorted without tuberculous infection of the bronchi. Prolonged collapse of the lung under either pneumothorax or thoracoplasty may lead to a foreshortened, widened, and tortuous bronchial tree which, from bronchograms, might suggest the presence of bronchiectasis. Extensive parenchymla scarring in the healing of the non-necrotic component of tuberculosis may on occasion lead to a similar situation.

However, under such circumstances, the morphologic appearance of either the bronchi or the lung parenchyma is not, in the writer's experience, comparable to that found in bronchiectasis in nontuberculous persons.

Parenchymal scarring not infrequently induces obstructive emphysema and the formation of bullae. Sometimes bronchi may become dilated as a result of their relationship to the area of scarring. Again, no evidence of abnormal development of either the bronchi or lung parenchyma is to be found. In this situation the dilatation of bronchi appears to be related to an obstructive element.

In the study of necropsies reported in an earlier chapter, there was the case of a twenty-five-year-old Negro woman who showed extensive tuberculous involvement of the lungs with multiple cavity formations. Of particular interest was an area in the apical portion of the left upper lobe which contained a number of empty cavities. The lung tissue in this region was of a bluish color, and no pleural adhesions were present over the area. Microscopic study showed that all of the cavities (Plate XXXVII, figure 115) were lined with columnar ciliated epithelium. The only evidence of tuberculous involvement was a localized necrotic mucosal lesion in one of the cavities. The lung parenchyma adjacent to the cavities was poorly formed and contained numerous histologic tubercles.

Study of the tuberculous disease in other portions of the lungs gave no evidence of old necrotic or calcific foci. The entire tuberculous disease gave one the impression that the extensive endobronchial dissemination arose from actively sloughing necrotic lesions which were of fairly recent origin.

In this case it would appear that a localized area of cystic bronchiectasis had later become infected to a slight degree with tuberculosis. This situation undoubtedly is rare. However, the case serves to illustrate that not all cavities in the upper chest can be attributed to tuberculosis.

A somewhat similar situation was found in a lung which was removed from a thirty-year-old Negro whose clinical history of tuberculosis dated back four years. Continuous chemotherapy during a two-year period had been given, and a marked clearing of roentgenographic shadows had occurred. Before treatment the sputum was copious and was positive for acid-fast bacilli; it had been reduced to a slight amount, however, and had become negative prior to surgery. Roentgenographic evidence of cavity formation persisted in both upper and lower lobes.

Macroscopic examination of the specimen showed a cavity in the apical posterior portion of the upper lobe which contained little debris and which had a

granular reddish to yellowish-gray inner surface. In this portion of the lobe there also were two smaller apparently clean cavities and a considerable amount of parenchymal scarring. In the lower lobe there were multiple clean, empty cavities and little macroscopic evidence of tuberculosis other than a few scattered small necrotic lesions.

Microscopic study of the upper lobe (Plate XXXVII, figure 116) proved the presence of a tuberculous cavity as well as the presence of two cystic bronchi which showed rather large areas of necrotic endobronchial disease. In addition there was an area in which broad bands of normal-appearing connective tissue were present, and in this area a number of bronchi had an overabundance of cartilage when compared with the size of the bronchi. Vessels of moderate size and normal structure were present in the area. Otherwise the lobe showed a considerable amount of parenchymal scarring and a few widely scattered small necrotic tuberculous lesions.

Study of the lower lobe showed that the cavity structures (Plate XXXVII, figure 117) were cysts lined with ciliated columnar epithelium. The walls of these cysts were composed of normal-appearing connective tissue with a few widely scattered bundles of smooth muscle. They were devoid of cartilage. In the contiguous tissue there was a considerable amount of connective tissue of normal structure, and blood vessels of moderate size with a normal structure were present. The cystic condition continued to the base of the lobe, and in this region some of the cysts showed a focal necrotic tuberculous ulceration of the mucosa. Otherwise the lobe showed some scattered parenchymal scars and an occasional small necrotic tuberculous focus.

This specimen showed a coexistence of cystic bronchiectasis and tuberculosis with some focal tuberculous ulceration of a few of the bronchial cysts. The cavity noted roentgenographically in the upper lobe was tuberculous in origin, and the one noted in the lower lobe represented a nontuberculous cystic bronchiectasis. This was the only resected specimen in the group under discussion in which cystic bronchiectasis was noted. The coexistence of these two pathologic processes certainly is uncommon. It does occur, however, and can confuse an interpretation of roentgenographically evident cavities.

In one case a posterior segment of an upper lobe and a superior segment of a lower lobe were resected. The segment of the lower lobe showed numerous large necrotic tuberculous lesions without evidence of bronchiectasis. The segment from the upper lobe showed an extensive amount of bronchiectasis and a few scattered necrotic tuberculous lesions. The majority of the ectatic bronchi (Plate XXXVIII, figure 118) were distended with a purulent exudate and showed extensive ulceration of the mucosa, whereas a few were free from infection and showed intact linings of columnar ciliated epithelium. Culture of the pus from the bronchi gave a growth of pneumococci. No acid-fast bacilli were seen on smear, and no growth of tubercle bacilli was obtained from these infected bronchi. However, growth of tubercle bacilli from the necrotic tuberculous foci was obtained. The interest in this case is that a nontuberculous infection was present in an area of bronchiectasis which was excised from a tuberculous patient.

In another case, a moderate-sized wedge of lung tissue was resected from both

upper pulmonary lobes. The tissue from one lung showed numerous necrotic tuberculous lesions and no evidence of bronchiectasis. The other specimen showed mostly bronchiectasis and only a few small tuberculous lesions. Some of the bronchiectatic bronchi contained mucopurulent exudate and others were empty. Of particular significance in this specimen was the finding of an empty, clean-walled, thin cystic space (Plate XXXVIII, figure 119) which measured eight millimeters in diameter. On microscopic examination, the epithelial lining was suggestive of the squamous epithelium of the esophagus. There was no evidence of ulceration or of scar tissue in the wall. No smooth muscle or cartilage was noted, and only a light infiltration with lymphocytes was found in focal areas. Perhaps this represents an unusual feature in bronchiectasis. The same condition, however, was found in two bronchiectatic specimens from nontuberculous patients.

In several of the specimens, the bronchiectatic process was of a limited extent and would have been overlooked had not a thorough examination been made. This situation was well shown by a right upper lobe which was removed from a twenty-five-year-old white female. There was a wide distribution of necrotic lesions in the lobe, with the major portion of the parenchyma free from disease. In the inferior and posterior portions of the posterior segment in an area which macroscopically appeared to be normal parenchyma, several empty thin-walled cystic areas lay just beneath the pleura. They were approximately one centimeter in diameter and showed a glistening grayish lining. Microscopic examination of this area showed no evidence of tuberculous involvement other than a few small parenchymal scars which probably represented healed non-necrotic tuberculous lesions. The cystic areas proved to be abnormally large and abnormally numerous bronchi for the area of parenchyma in which they were located. These bronchi (Plate XXXVIII, figure 120) were devoid of cartilage, showed no cellular inflammatory reaction, and were lined with a normal columnar ciliated epithelium. Small mucous glands were associated with two of the bronchi. The distribution of smooth muscle was erratic; it was absent in some areas and abundant in others. Such a condition was found in most of the bronchi. No evidence of an obstructive process was found proximal to the large bronchi. In this specimen a marked aberration in development of bronchi was present in a limited area in which no evidence of tuberculosis was found other than a few small parenchymal scars which were too small to have any effect on the production of the bronchiectatic condition.

Extensive bronchiectasis was present in a few of the specimens. One such specimen was a lower lobe removed from an eighteen-year-old white female. This woman had raised a considerable amount of mucopurulent sputum from which, on occasion, only a few colonies of tubercle bacilli could be grown. The roentgenographic shadows were more suggestive of a bronchiectatic condition than of tuberculosis. Macroscopic examination of the specimen showed a number of widely scattered necrotic tuberculous lesions, the largest of which was directly associated with a large cystic space which was filled with purulent exudate. Acid-fast bacilli in small numbers were found in this exudate. Another large

cystic space was also filled with purulent exudate, and no acid-fast bacilli were found. In addition there were several large thin-walled cystic areas which contained no exudate and which had smooth, glistening, grayish linings.

Microscopic study of numerous sections from different portions of the lobe showed a widespread dissemination of necrotic and non-necrotic tuberculous foci. Only an occasional lesion was larger than five millimeters in diameter. Only a few small widely scattered parenchymal scars were found. There was less well-developed lung parenchyma than one would expect to find in a normally developed lobe.

The bronchial pattern was the most interesting portion of the specimen. No evidence of an obstructive element was found. There were many large cystic bronchi, all of which had either cuboidal or columnar ciliated epithelial linings. The majority of these bronchi showed no inflammatory reaction in the mucosa. Some contained little connective tissue in their walls, whereas in others the connective tissue was abundant. Rarely was any cartilage or smooth muscle found. A few of the large bronchi contained necrotic debris, and these showed focal necrotic endobronchial lesions. A large, thin-walled bronchus (Plate XXXIX, figure 121), which was directly associated with a seven-millimeter necrotic parenchymal tuberculous lesion, showed marked lymphocytic infiltration of the mucosa and focal necrotic tuberculous ulceration. Except for the areas of ulceration, the columnar ciliated epithelial lining was intact. An occasional giant cell and small histologic tubercle were present in the mucosa. The other pus-containing cystic bronchus, which was at the base of the lobe, showed an intact ciliated epithelial lining without evidence of tuberculous lesions.

From the study of this specimen it appeared evident that the cystic bronchiectasis had become involved, in part, by the tuberculous infection; in part, by a nontuberculous infection; and, to a greater extent, had not become infected with either.

The presence of necrotic endobronchial tuberculosis in some of the cystic bronchi was of serious import for the reason that lesions of this nature are most difficult to heal. The majority of the tuberculous lesions were parenchymal and were distributed in the same manner as lesions in a nonbronchiectatic lung. No tuberculous lesions were found which would indicate that the infection was of long duration. To the writer, it seems unlikely that the bronchiectasis can be related etiologically to either type of infection. Once such abnormal bronchi become infected, however, a disposal of the infection presents a difficult problem. Of the two infections, tuberculosis presents the most difficult problem because of the production of necrotic endobronchial lesions.

A somewhat similar condition was encountered in the lower and middle lobes of a lung which was removed from a forty-year-old white female. In this case bronchiectasis had not been suspected clinically. Because of wheezing on occasion, endobronchial tuberculosis was suspected. However, bronchoscopy failed to reveal any endobronchial disease. The patient raised only scanty amounts of sputum, which was mostly of a mucoid type and which occasionally yielded growth of a few colonies of tubercle bacilli.

The upper lobe showed scattered foci of tuberculosis, and there was no evidence of bronchiectasis. A bronchial branch which led to a small filled-in cavity showed a moderate degree of stenosis due to organizing necrotic endobronchial tuberculosis. There was less parenchymal tuberculosis in the middle and lower lobes; however, there was extensive bronchiectasis. Several of the ectatic bronchi contained necrotic material and showed a considerable amount of necrotic endobronchial tuberculosis. Other ectatic bronchi were empty, had normal ciliated epithelial linings, and showed no evidence of infection. To a large degree all of the abnormal bronchi, whether infected or not, showed a rather large wall of connective tissue, were devoid of cartilage, and had little smooth muscle. Between these bronchi there were broad bands of connective tissue in which there were sizable blood vessels of normal structure, an occasional nerve fiber, and an occasional bundle of smooth muscle. With such a structure, the connective tissue can hardly be considered to be scar tissue.

Near the base of the lobe, a group of four firm nodules occupied an area of approximately two cubic centimeters. These proved to be cysts (Plate XXXIX, figure 122) filled with clear mucus. They were lined by markedly flattened ciliated epithelium and appeared to be bronchiogenic cysts. A similar condition was observed in two other bronchiectatic specimens.

Another specimen was a right lung which was removed from a forty-two-year-old white female. Advanced tuberculosis with cavity was diagnosed at the age of forty years. There had been two episodes of small pulmonary hemorrhage and blood-streaking of sputum. There had been episodes of pneumonia dating back to childhood. However, no diagnosis of bronchiectasis had been entertained. A thoracoplasty was performed, after which larger amounts of mucoid and mucopurulent sputum were raised, and two small pulmonary hemorrhages occurred. The sputum continued to contain a small number of bacilli. Bronchoscopy showed mucopurulent secretions in the middle lobe bronchus and no evidence of endobronchial tuberculosis. Seven months after thoracoplasty the right lung was resected.

Examination of the upper lobe showed two filled-in cavities with patent bronchial communications, a few scattered necrotic tuberculous lesions, scattered parenchymal scars, and no evidence of bronchiectasis.

Examination of the middle and lower lobes showed extensive bronchiectasis throughout both lobes and only a few widely scattered small necrotic tuberculous lesions. No evidence of stenosis or other obstruction in the bronchi was found. A considerable amount of mucus was present in the bronchi. No cystic dilatations of bronchi were found, but the bronchi were abnormally large to the periphery of the lobes. Little evidence was found of cartilage in the bronchial walls, so that for the most part they were in a collapsed state. The parenchyma was rather emphysematous and of delicate structure, with a few scattered scars. An old obliterative pleuritis was present.

Microscopic examination revealed nothing of unusual character in the tuberculous process. Only a few of the ectatic bronchi, more in the middle than in the lower lobe, showed infection with focal ulceration. It seemed plausible that the

small pulmonary hemorrhages may have arisen from the areas of bronchiectasis which had undergone ulceration rather than from the tuberculous lesions. The majority of the ectatic bronchi (Plate XXXIX, figure 123) were well supplied with smooth muscle, but little evidence of cartilage was found. Some of these structures, even well out in the lung, had an abundance of mucous glands. In many, a rather large portion of the cells in the epithelial lining had the appearance of goblet cells of the gut rather than of bronchial epithelium. In other bronchi a lining of normal ciliated columnar epithelium was noted. No evidence of tuberculous infection was found in any of these abnormal bronchi.

A left lung removed from a forty-year-old white male proved of particular interest because of the clinical history. Beginning at the age of sixteen, this patient had raised from thirty to ninety cubic centimeters of mucopurulent sputum in the morning. This condition was worse during the fall and winter months. At the age of thirty-seven, pulmonary tuberculosis was diagnosed, and bronchographic studies revealed bronchiectasis of the lower lobe. Bronchoscopy revealed an ulceration and a slight stenosis of the main bronchus. This was treated by topical applications, and the ulcerated area appeared to heal. Bronchoscopy prior to removal of the lung showed the main bronchus to have a lumen of approximately one-half normal size.

The upper lobe was about twice the size of the lower lobe. In it there were rather widespread necrotic lesions and an open tuberculous cavity. The bronchial system was of normal proportions. Some of the bronchial branches showed an inflamed and thickened mucosa, especially in the portion of the lobe that contained the cavity. There was no macroscopic evidence of necrotic endobronchial tuberculosis, and no evidence of bronchial stenosis was found.

In the abnormally small lower lobe, two basal segmental bronchi showed ulceration and considerable stenosis. The other segmental bronchi were all of normal proportions at the point of origin. The bronchial pattern of the superior segment was normal. In all basal segments the bronchi were all unusually large. They were no larger beyond the area of stenosis than in the other segments. The bronchial branches beyond the stenoses, however, contained necrotic and mucopurulent secretions, whereas in the other basal segments they contained secretions which were more mucoid than purulent.

Microscopic study of the upper lobe showed no evidence of necrotic endobronchial disease. Some of the bronchi showed extensive lymphocytic infiltration of the mucosa and a few histologic tubercles and giant cells.

The ectatic bronchi (Plate XL, figure 124) of the lower lobe showed extensive necrotic tuberculosis of the branches beyond the stenosed bronchi. In some of these bronchi, bits of necrotic cartilage lay in the necrotic debris within the bronchial lumen. The bronchial branches in the other basal segments showed focal necrotic ulcerations, but to a considerable degree the epithelial lining of these bronchi was intact.

It appears probable that bronchiectasis of the left lower lobe was present at the age of sixteen, although the condition was not recognized until twenty-one years later. The tuberculous infection of this bronchiectatic lobe has two fea-

tures of particular interest. Partial and unhealed tuberculous stenosis of two of the basal segmental bronchi was present, whereas the other segmental bronchi were not so affected. Also the ectatic bronchi beyond the stenosis were much more severely and extensively involved in necrotic endobronchial disease than were the other ectatic bronchi.

The final specimen to be discussed was a right upper lobe which was resected from a twenty-year-old white male. This patient had been treated for advanced pulmonary tuberculosis with multiple-drug therapy for two years. Considerable clearing of roentgenographic shadows occurred; however, the upper lobe appeared to be shrunken and more dense than was normal.

Macroscopic examination of the small shrunken lobe showed a complete roughening of the pleura by adhesions and a lobar bronchus of normal proportions and appearance. The lobe was firm and without palpable nodules. Only a few three-millimeter necrotic lesions were found. There was a considerable amount of grayish nonpigmented connective tissue, and many interlobular septae were unusually thick. Also there were moderate-sized foci of parenchymal scarring, and in these areas anthracotic pigment was present. No evidence was found of a residual tuberculous cavity.

The most interesting feature of the specimen was the presence of numerous clean bronchi, some of which were as large as one centimeter in diameter. No evidence was found of obstruction to, or stenosis of, any bronchi.

Microscopic examination revealed a few small necrotic parenchymal tuberculous foci and rather extensive parenchymal scars in which a moderate amount of anthracotic pigment was present. These scars would seem to represent a healed non-necrotic tuberculous pneumonia. There were broad bands of connective tissue of normal structure, without any deposition of anthracotic pigment. Several of these structures appeared to be abnormally thick interlobular septae in which blood vessels of moderate size were present. Tissue of this structure occupied approximately half of the volume of the lobe. It did not seem to be related to the tuberculous disease.

The large bronchial and cystic structures extended from the hilar region to just beneath the apical pleura (Plate XL, figure 125). They were all devoid of cartilage and showed little smooth muscle. Most of them were lined with columnar ciliated epithelium and showed no evidence of cellular infiltration of the mucosa. Some were spaces without any epithelial lining which were also devoid of cellular infiltration of the walls. That these cystic spaces were a part of the bronchial system was indicated by the finding of a bronchus near the hilum which had a normal epithelial lining up to the point of its wide opening into a cystic space without epithelial lining. In one of these unlined cystic bronchi, a focal necrotic tuberculous ulceration was found.

In this case it would appear that bronchiectasis was present prior to the occurrence of the tuberculous disease. However, no clinical evidence suggestive of the condition could be elicited from the patient even after the pathologic evidence had been produced.

GENERAL COMMENT

A literal translation of the term bronchiectasia or bronchiectasis connotes abnormally large bronchi. As bronchi are not rigid tubes, it would seem that during some phase of respiration normal bronchi might be distended with air and a temporary bronchiectasis would be present, if one chooses to be literal. To be sure, this is not the sense in which the term is used. The term in itself is devoid of any etiologic implications. The difficulty encountered in the use of the term is that, commonly, etiologic factors have been read into an interpretation of an observed phenomenon. Often the interpretation has been based solely upon clinical manifestations and bronchographic findings. It seems unlikely that this term, because of common usage, can be replaced by another, although a different nomenclature might be advisable.

A brief discussion of the conditions which may affect bronchi so that an abnormal pattern may be seen in bronchograms might, to some extent, clarify the situation. Any factor which obstructs a bronchus conceivably can cause distention of bronchial branches distal to the point of obstruction. This distention can be caused by either retention of normal secretions or of an inflammatory exudate plus the normal secretions. The writer has observed this phenomenon due to tumor growth within a bronchus; to stenosis in the process of repair of necrotic endobronchial tuberculosis; and to compression and distortion of a normal bronchus which is intimately involved in scars resulting from the organization of non-necrotic tuberculous pneumonia. It is claimed that bronchi may be obstructed from external pressure by enlarged tuberculous lymph nodes. Although the writer has seen numerous fairly large tuberculous lymph nodes in adults, he has not found an instance in which these nodes have caused an obstruction of bronchi.

A considerable diminution in the size of the lumen of a bronchus is necessary before bronchial branches distal to the obstruction can be distended by retained material. In these conditions, bronchograms would not reveal the enlarged bronchi, since the bronchial lumen is markedly narrowed and the distended bronchi already are filled with secretions. This condition, when found on examination of a specimen, might be called bronchial distention distal to an obstruction rather than bronchiectasis.

A normal bronchial pattern may be distorted by extensive parenchymal scarring in the organization of non-necrotic tuberculous pneumonia and in the organization of nontuberculous pneumonias. Moreover, in tuberculous lungs under prolonged pneumothorax or under thoracoplasty, the bronchi may become foreshortened and tortuous because of the prolonged extensive collapse of the lung. Under these conditions bronchograms may show an enlarged and abnormal bronchial pattern, although the bronchi may have a normal structure. Such a condition indicates a distortion of the bronchial pattern rather than bronchiectasis.

In the discussion of bronchial lesions in tuberculosis, it was pointed out that bronchi well out in the lung might become occluded with necrotic material dis-

persed endobronchially from sloughing lesions. As the lumina of these bronchi are already filled, bronchograms might reveal an altered pattern with areas suggestive of dead limbs on a tree.

This brings us to a consideration of the specimens which have been discussed above. There are three features which all of the specimens have in common. No obstructive element is present; abnormally large bronchi are always found; and these are lined, with rare exception, by columnar ciliated epithelium.

Apart from these three features, considerable variation exists between specimens. The extent of the process ranges from a relatively small area of a segment to complete involvement of one or more lobes. In some specimens there are no cystic dilatations, and in others large cysts are the outstanding feature. In an occasional specimen the abnormally large bronchi contain an overabundance of cartilage, whereas in most instances cartilage is either meager in amount or entirely lacking. There is a paucity of smooth muscle in the majority of bronchi, whereas, in some, an overabundance of this element is present. Sometimes a single large bronchus with no evidence of infection has an abundance of smooth muscle in one part and none in another. In a few instances, fairly large mucous glands are associated with large bronchi which are devoid of cartilage and of smooth muscle and are located well beyond the area of lung in which bronchial mucous glands are normally present.

In two specimens the epithelial cells which lined the large bronchi evidently were secretory cells, and these were present in bronchi just beneath the pleura at the most distal portion of the lobe as well as in other areas. Fat tissue in association with cartilage was present in two instances in large bronchi near the pleura. In two specimens with large cysts, small bronchi with a superabundance of cartilage and sizable mucous glands were found in adjacent lung tissue well out toward the periphery of the lobe. Small bronchiogenic cysts which were filled with clear mucus under pressure were associated with large open bronchi in three specimens. In two specimens, clean and empty cystic spaces were found to be lined by a stratified squamous epithelium which closely resembled the epithelial lining of an esophagus.

When all of the variations which are found in bronchial structure are taken into account, it would seem to the writer to be most difficult to explain them as sequelae to any infectious process. It would seem that the microscopic variations observed might well be of as great importance as the macroscopic evidence of abnormally large bronchi in obtaining an understanding of the pathologic process.

The variations in pulmonary structure are not limited to the bronchi. In some specimens there is an abundance of pulmonary parenchyma which most often is delicate in structure and tends to be emphysematous, whereas in other specimens there is little pulmonary parenchyma. Evidence of parenchymal scars which would represent organized pneumonia usually are lacking in the latter specimens. In two specimens, large thin-walled clean cysts which are lined to a great extent with cuboidal epithelium are present in an abundant emphysematous lung parenchyma. In a few instances, small, poorly developed lobules which are suggestive more of a fetal than an adult structure are present.

It is common to find rather broad bands of normal connective tissue in which moderately large blood vessels of normal structure are frequently noted. These are considered to be interlobular septae, as there is no evidence of parenchymal scarring in adjacent areas Also there sometimes is an overabundance of connective tissue in

other areas, and in the connective tissue frequently there are moderately large and numerous blood vessels. Sometimes normal nerve fibers are found, and in a few instances considerable amounts of smooth muscle are present in focal areas. These findings hardly would be expected in scars which have replaced lung parenchyma.

In several specimens it is apparent that blood vessels are unusually abundant. In some instances a fibrotic thickening of the intima of the vessels is easily found, and in other instances all of the vessels have normal structures. The cause of the intimal thickening is not apparent.

Extensive obliterative pleural adhesions are present over the bronchiectatic specimen in some cases and, in some, no evidence of pleural adhesions is found. In both conditions evidence of infection of the bronchiectatic process is present. The reason for the presence or absence of pleural adhesions is not apparent, although, when present, it may be assumed that a pleural involvement accompanied the occurrence of a pneumonia.

Evidence of nontuberculous infection is present in all of the specimens that were removed subsequent to a clinical diagnosis of either bronchiectasis or chronic lung abscess. However, there are some specimens in which all of the abnormal bronchi are not infected. Evidence of mucosal ulcerations is frequently observed, and these ulcerations reveal the same morphologic picture which is found in mucosal ulcerations in normal bronchi. In a few specimens there is evidence of healing of ulcers and, here, there is a growing out of stratified squamous epithelium over the healing ulcer from the normal bronchial epithelium which abuts upon the focal area of ulceration. This same phenomenon may be found in the healing of necrotic endobronchial tuberculosis in specimens in which no evidence of bronchiectasis is found. The same phenomenon is present in the single case of a chronic pulmonary abscess which was discussed above.

The lack of uniformity rather than the similarity between specimens is stressed for the reason that usually it is the bronchial and vascular structures which are the center of discussion in bronchiectasis. It is believed that it is essential to consider a bronchiectatic lobe as a whole, for the bronchial system and the lung parenchyma are inextricably bound together as a functional unit without any barrier between the bronchus and the terminal alveoli.

The outstanding feature of all bronchiectatic specimens is the presence of abnormally large bronchi which are uniformly lined with a normal bronchial epithelium. With the exception of focal ulcerations, this feature persists even if the bronchi are full of purulent exudate and even if the clinical history indicates that the condition has existed for years. The mode of origin of these bronchi is the focal point about which a diversity of opinion centers.

One of the commonly accepted concepts of bronchiectasis is that during childhood an episode of necrotizing bronchitis occurs, usually as a complication of measles or whooping cough. It is postulated that a plug of secretions develops in the larger bronchi, with a necrotizing bronchitis beyond this obstruction. Moreover, some students believe that, in children, tuberculous lymph nodes obstruct the bronchi by pressure and a necrotizing bronchitis occurs distal to the point of obstruction. The necrotizing process supposedly brings about a destruction of the smooth muscle and of the elastic tissue of the bronchial walls and, be-

cause of this situation, the elasticity and the contractability of the bronchi are lost. In such a necrotizing process it would seem unlikely that the epithelial lining would also escape destruction. As the dilated bronchi in bronchiectatic specimens are nicely lined by normal bronchial epithelium, it would appear that a normal epithelium had grown out to cover the denuded surface in the healing of the necrotizing bronchitis. The abnormally large bronchi not infrequently extend from the hilar region to just beneath the most distal pleura, and it would appear that under such circumstances the necrotizing bronchitis initially would have to be extensive. Moreover, after the healing of the necrotizing bronchitis, these bronchi must grow, for they become much larger and longer than the normal bronchi of a young child. These features, it is believed, cover the essential concepts of those who regard the development of bronchiectasis as a sequel to a necrotizing bronchitis.

In the present data it is clear that all ectatic bronchi do not lack smooth muscle. In the writer's opinion, it is the lack of smooth muscle rather than the meager amount of elastic tissue that permits a permanent dilatation of bronchi. The finding of ectatic bronchi with an abundance of smooth muscle would seem to blunt the concept that it is the destruction of this tissue which permits bronchi to become ectatic.

The only unquestionable evidence of an epithelial re-covering of ulcerated bronchial walls which the writer is able to produce is the finding of squamous epithelium growing out over the cleansed granulation tissue. This has been observed in both necrotic endobronchial tuberculous lesions and in ulcerated ectatic bronchi. The finding does not refute the idea that a normal epithelium may recover a once ulcerated surface. From the writer's studies, it seems that this would be unlikely if much tissue of the bronchial wall beyond the epithelial layer had been destroyed.

It is interesting that failure to find elastic tissue, smooth muscle, mucous glands, and cartilage in ectatic bronchi is usually regarded as evidence that these elements have been destroyed by an infectious process. The possibility should be suggested that these elements may never have been present. This suggestion is offered because the writer has seen ectatic bronchi in which there was no evidence of inflammation or of scar tissue and in which these elements also were lacking. In necrotic endobronchial tuberculosis, a process which is much more severe than any found in bronchiectasis, one not infrequently finds that mucous glands, cartilage, and smooth muscle remain intact beyond the zone of necrosis. It is believed that absence of the tissue elements under consideration can be ascribed to aberrations in development as logically as it can be postulated that they are destroyed during the course of an infection.

In the twenty-seven specimens in which tuberculosis and bronchiectasis coexisted, evidence of tuberculous infection of the abnormal bronchi with the presence of necrotic endobronchial ulceration was found in seven. In these cases many of the abnormal bronchi showed no evidence of infection. In ten specimens there was evidence of a nontuberculous infection of the bronchiectatic area.

Some of the abnormal bronchi in three specimens were infected with tuberculosis; others, with a nontuberculous infection; and there was no evidence of infection in others. In the remaining seven, the bronchiectatic area showed no evidence of either tuberculous or other infection.

The writer's interest in the nature of bronchiectasis stemmed from the unexpected finding of this condition in specimens resected from tuberculous patients and from the fact that the process did not appear to be related to tuberculous infection. On the other hand, abundant evidence was found that necrotic endobronchial tuberculosis does not terminate in a process which resembles nontuberculous clinical bronchiectasis. The stenosis which occurs in the process of healing of necrotic endobronchial tuberculosis leads to obstruction, with retention of secretions beyond the point of obstruction. It would seem to the writer that a similar situation would arise following the repair of marked destruction of bronchial walls in other infections. This situation was not encountered in any of the nontuberculous bronchiectatic specimens.

From the examination of bronchiectatic specimens removed from nontuberculous patients, it would appear that infection is always present, for a bronchitis with or without ulceration of the mucosa was found. Examination of the specimens removed from tuberculous patients showed that bronchiectasis can occur without evidence of infection. Perhaps this difference is due to the selection of patients for operation. Usually a clinical diagnosis of bronchiectasis is arrived at only after there is a lengthy history of raising of sputum, or of repeated episodes of pneumonia, or of unexplained pulmonary hemorrhages. It would appear likely that a noninfected bronchiectasis would be clinically silent because the bronchi contain no secretions and evidence of bronchitis is lacking. On this basis it is easily understood why bronchiectasis has come to be regarded clinically as a suppurative disease of bronchi and, as a corollary, why bronchiectasis has come to be regarded commonly as a progressive disease.

The tuberculous specimens included in the present discussion were obtained at stages of disease that previously had been unavailable for study; hence, a thorough macroscopic and microscopic examination of each specimen became a routine procedure. The bronchiectatic specimens removed from nontuberculous patients were examined with equal thoroughness. As the number of observed anatomic variations accumulated, it appeared that the aberrations in the morphology both of bronchi and of lung parenchyma could hardly be sequelae to an infectious process.

In order that the pathologic process under discussion may be separated from bronchial conditions which may result from either obstructive or distortional factors, the writer suggests the term *developmental bronchiectasis*. Under this designation would be placed *cylindrical bronchiectasis; saccular bronchiectasis; cystic bronchiectasis; cystic disease of the lung;* and *small well-localized bronchiectatic processes* which are found on occasion. All of these conditions may be regarded as a difference in the degree of abnormal development of the lung structure.

Since bronchiectasis, as commonly understood, has not been observed in full-

term infants and only rarely during the first year or so of life, it would seem that this condition becomes evident only with the post-natal growth of the lung. If this condition is linked to the growth of the lung, then it would seem that the complete development of the process would be attained with the full growth of the individual. Progression of bronchiectasis would seem, on this basis, to be unlikely after maturity is reached.

The etiologic factors which are concerned with developmental bronchiectasis are unclear. Agenesis of the lung or of a lobe of lung are on occasion found at birth. In one specimen in the group under discussion, agenesis of a right middle lobe was associated with an extensive bronchiectasis of a right lower lobe. Bronchiogenic cysts are also found on occasion in infants. In 3 cases in this series, bronchiogenic cysts were associated with bronchiectasis. On occasion cystic disease of the lung has been observed at birth. Perhaps cystic bronchiectasis is related directly to congenital factors. There are these situations which suggest that perhaps bronchiectasis, as commonly observed, may also be related to congenital factors. On the other hand, this probably is not the complete story. Perhaps an irreparable damage to lung parenchyma, such as an organized pneumonia, early in life might make it impossible to have a normal development of lung parenchyma. Under these circumstances, a normal bronchial structure might be present and could continue to grow until maturity is reached. In the course of development, aberrations in bronchial structure conceivably could occur. However, in such specimens, evidence of an organized pneumonia should be present. The writer has not observed a specimen which would fit such a situation.

Despite the obscurity of the etiologic factors, it seems that developmental bronchiectasis is an irreversible process. Conceivably, inadequate pulmonary function could be linked to developmental bronchiectasis, provided that the process were of sufficient extent. It is well known that the chronic suppuration which commonly is associated with this condition can be debilitating and may have even more serious implications. Tuberculous disease in ectatic bronchi is difficult to eradicate because necrotic endobronchial disease develops, and this process is an extremely stubborn one to heal. Developmental bronchiectasis may be found in all lobes of the lungs, and this needs careful consideration in the management of the patient.

Tuberculous disease may give rise to distortion of bronchi which would be demonstrable in bronchograms. It may also induce distention of bronchi distal to an obstruction. These distended bronchi would not be revealed in bronchograms. Finally, it is, on occasion, associated with developmental bronchiectasis without there being any etiologic relationship. This condition should always be demonstrable bronchographically, provided that the contrasting medium flows into the area in which the ectatic process is present.

PLATES XXXII–XL follow

PLATE XXXII

FIGS. 97, 98, 99, and 100. (× 5)

FIG. 97. Section of lung from five-month stillborn fetus. Note the numerous epithelial-lined tubules which extend to the pleura in the upper portion of the illustration. The large tubules probably are destined to be the bronchial tree and the smaller ones to be the area of development of lung parenchyma. The line of separation to the right is the fissure line.

FIG. 98. Section of lung from seven-month stillborn fetus. There are many more small epithelial-lined tubules, proportionally, than larger ones at seven months than at five months. Lobular development is now evident, and the pleura is a definite structure. Note again that the small tubules extend to the pleura.

FIG. 99. Section from lung of fetus of approximately same age as that shown in figure 98. Fetus lived one day. Note that now the small epithelial-lined tubules have become alveoli.

FIG. 100. Section of lung from premature infant who lived thirteen days. Infant approximately seven and one-half months old at birth. Death was due to cardiac anomaly. The bronchial system forms a minor portion of the tissue, and practically all of the smaller tubules have become well-formed alveoli. Some are so large that they suggest an emphysematous condition.

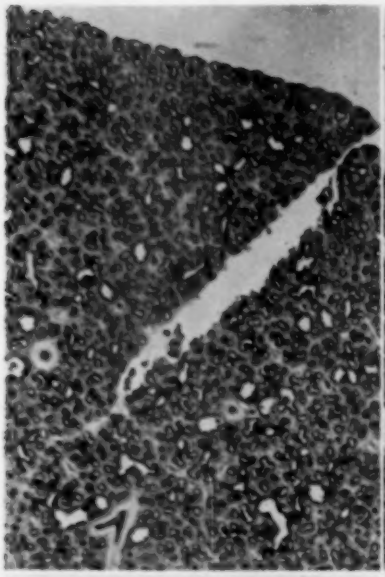


FIG. 97

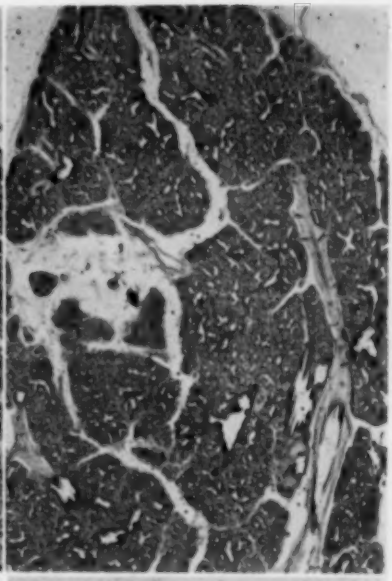


FIG. 98

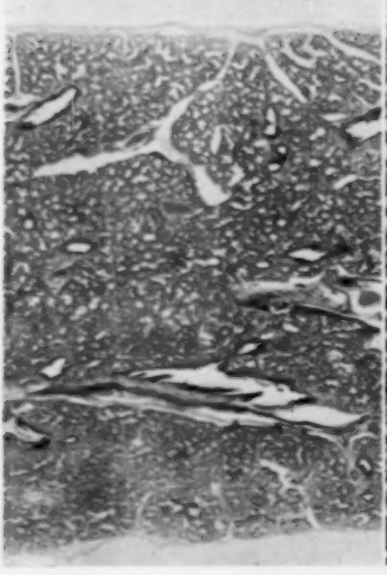


FIG. 99

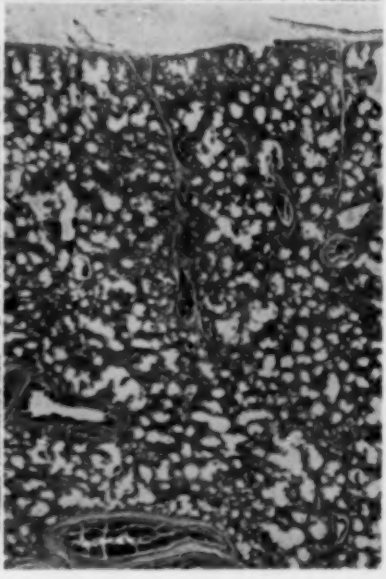


FIG. 100

PLATE XXXII

PLATE XXXIII

FIG. 101 (× 4). White male, sixty-two years of age. Case discussed in text. Illustration from area approximately 5 mm. from the diaphragmatic pleura. The two bronchial branches in the lower left-hand corner are subdivisions of the segmental bronchus which was abnormally formed and ulcerated at its origin. All branches of this segmental bronchus showed a marked lymphocytic infiltration of the mucosa, had many focal mucosal ulcerations, and contained some mucopurulent exudate. The two branches in the illustration are typical of all of the bronchial branches of this segment of lung. Note the moderately large pieces of cartilage associated with fat tissue. This condition is sometimes found in the hilar region, but it is distinctly abnormal so near the diaphragmatic pleura.

The remaining bronchial branches are subdivisions of the other basal segmental bronchi. None of these bronchi showed evidence of infection. However, they are similar in structure to the infected bronchi. The large bronchus in the upper central portion shows large pieces of cartilage with an association with fat in some. Mucous glands are present, and this is another abnormal finding, considering the location of the bronchus. Note the peculiar cluster of thin-walled bronchial branches at the lower right of the large bronchus. Note also the thin wall and lack of cartilage in some of the other bronchi and the presence of several moderately large blood vessels. Other than some emphysema, the lung parenchyma is not unusual. There is little smooth muscle in any of the bronchi.

FIG. 102. (× 3) White female, fifty-six years of age. Discussed in text. Illustration shows general morphologic character of the specimen. The two large cystic areas have no cartilage or muscle in the walls. The distended one was full of mucopurulent secretions; the collapsed one contained no secretions. Some bronchi showed no cellular inflammation in the mucosa, whereas others showed a marked lymphocytic infiltration. Focal ulceration was absent in most bronchi, but was considerable in others. The area in the lower left-hand quadrant, directly above two bronchial branches, shows a number of small tubules which were lined with cuboidal epithelium. This area was suggestive of fetal lung tissue. Several other similar areas were noted. In one area, two empty thin-walled cysts were lined by squamous epithelium suggestive of that commonly seen in the esophagus. These cysts showed no scar tissue about them and no cellular inflammation. Illustration came from lower third of the pulmonary lobe. Note that normal lung parenchyma is present, but this was much less than would be found in a normal lung. There was little evidence of the type of scarring that is common in organized pneumonia.

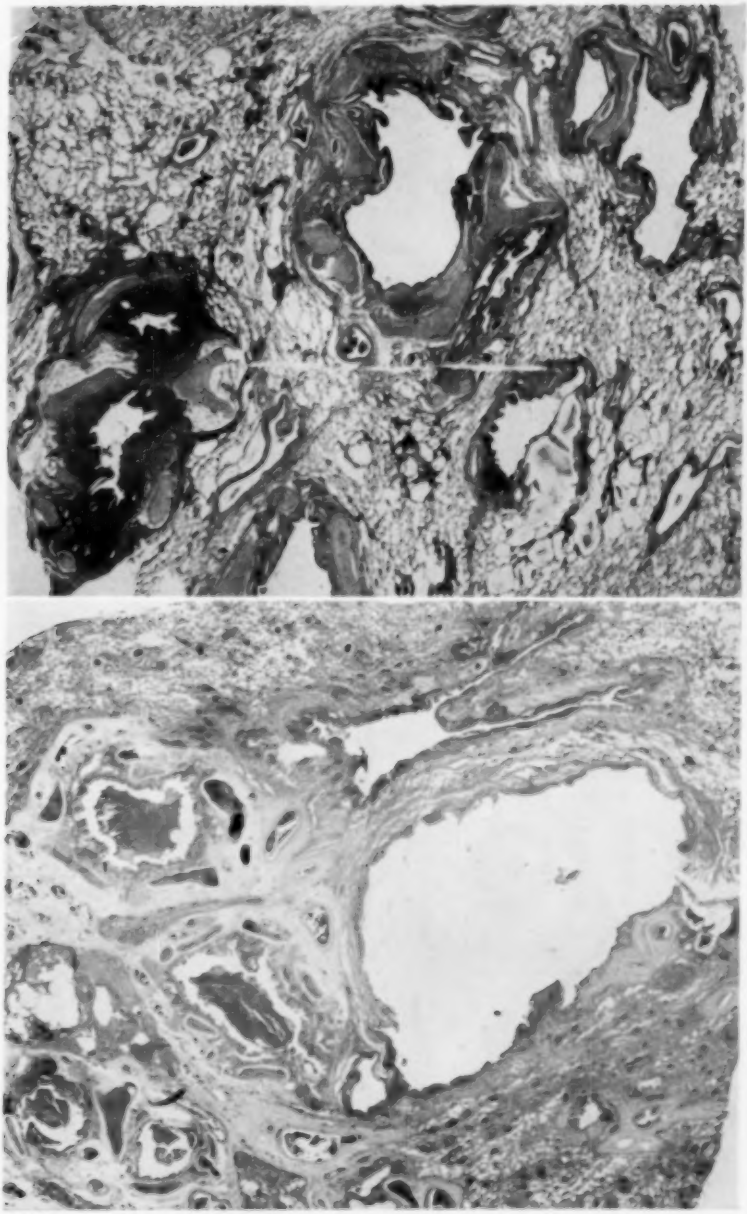


FIG. 101

FIG. 102

PLATE XXXIII

PLATE XXXIV

FIG. 103. White female, thirty-one years of age. Discussed in text. Actual size on cross-section of resected middle lobe. No pleural adhesions were present. The tissue is mainly composed of large bronchi.

FIG. 104. (× 3) Section from lobe shown in figure 103. The large bronchus running lengthwise had abundant cartilage except in its distal portion. The lumen appeared narrowed as one looked into the bronchus at the resected end. This narrowing was found to be due to projections from the wall which gave the lumen a tortuous course. The large bronchus at the upper center showed no smooth muscle, no cartilage, marked lymphocytic infiltration, and focal ulcerations of the mucosa; aside from the ulcerated areas, it had a ciliated columnar epithelial lining. The many bronchial branches in the upper right quadrant were similar in structure, but showed no inflammatory reaction in the mucosa. There was little pulmonary parenchyma, and no evidence of an organized pneumonia was found.

FIG. 105. (× 4) White male, sixty-four years of age. Discussed in text. The large cystic bronchi were empty. They showed no cartilage and very irregular distribution of smooth muscle in the walls. The broad bands of connective tissue which formed the bronchial walls had the structure of normal connective tissue rather than of scar tissue. All of the abnormal bronchi were lined with ciliated columnar epithelium. There was an abundant delicately formed lung parenchyma. Illustration from near the diaphragmatic surface of the lower lobe.

FIG. 106. (× 4) Section of middle lobe resected from patient shown in figure 105. The lobar bronchus has been cut into. Aside from the bronchus, the tissue was composed entirely of normal-appearing connective tissue and blood vessels. This association of agenesis of one lobe and bronchiectasis of another lobe may be fortuitous; on the other hand, this association may have significance.

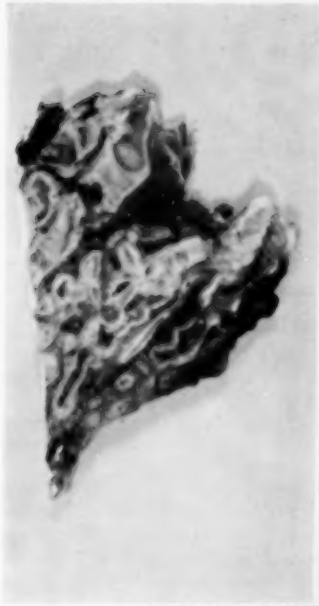


Fig. 103

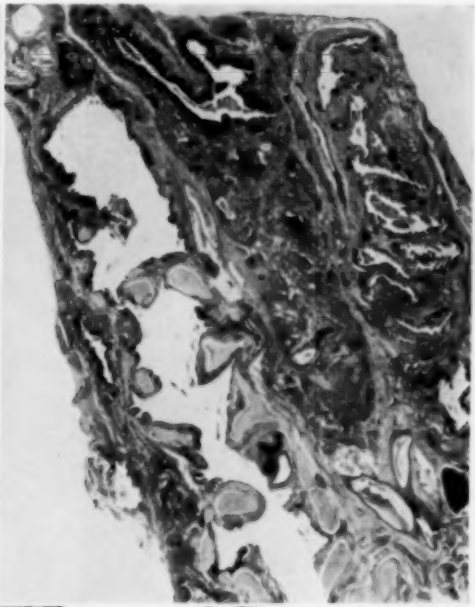


Fig. 104

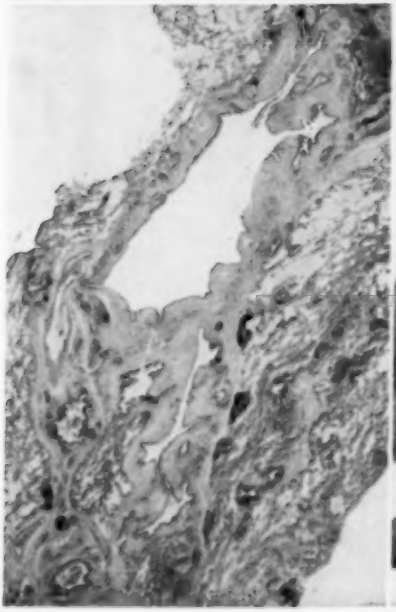


Fig. 105

Fig. 106

PLATE XXXIV

PLATE XXXV

FIG. 107. (× 5) White female, twenty-five years of age. Several years' history consistent with bronchiectasis clinically, with occasional small pulmonary hemorrhages and blood-streaking of sputum. The bronchiectatic process was confined to the inferior portions of both segments of the middle lobe. The large bronchus in the illustration is ulcerated. Note the prominence of the bronchi, all of which show marked lymphocytic infiltrations of the mucosa. The small size of the pulmonary lobules and the small amount of lung parenchyma also are distinctly abnormal. There was no evidence of an organized pneumonia. Many of the small open spaces are lined with cuboidal epithelium, suggestive of the condition found in a developing fetal lung.

FIG. 108. (× 15) White male, fifty-six years of age. Left upper lobe removed on a clinical diagnosis of chronic pulmonary abscess. Case discussed in text. Illustration is from the large cyst which showed extensive ulceration. At the bottom the epithelial lining is of the ciliated columnar type. In the upper two-thirds, the lining is of the stratified squamous type. In the opinion of the writer, this type of epithelial metaplasia is a constant feature in the recovering of ulcerated bronchi in which the ulceration has extended beyond the mucosa.

FIG. 109. (× 15) From the same specimen shown in figure 108, a small bronchus near the pleura of the posterior surface of the lobe. Note the large cartilage, the mucous glands, and the small size of the bronchial lumen. The epithelial lining is of the ciliated columnar type. The bronchus not only has an abnormal structure, but is also in a location in which mucous glands and large pieces of cartilage are not found in a normal lung.

FIG. 110. (× 3) White male, thirty-five years of age. Case discussed in text. Illustration is from an area near the diaphragmatic surface of the lobe. The large cystic space is lined with ciliated columnar epithelium and has no smooth muscle. There were several cysts of this magnitude, some of which were lined with cuboidal epithelium.

Fig. 107

Fig. 108

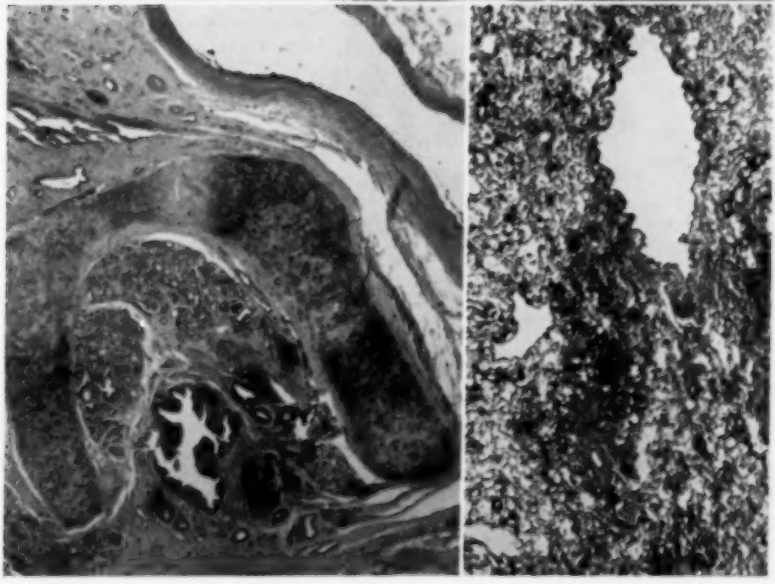


Fig. 109

Fig. 110

PLATE XXXV

PLATE XXXVI

FIG. 111. (× 15) Negro male, forty-five years of age. Case discussed in text. Illustration shows considerable areas of inner surface of cavity wall covered with stratified squamous epithelium and also areas which have no epithelial covering. In no place was a lining of columnar ciliated epithelium found. To the writer the situation observed in this case definitely separates the condition from cystic bronchiectasis, which clinically is usually diagnosed as a chronic lung abscess.

FIG. 112. (× 4) White male, sixty-two years of age. Case discussed in text. Illustration shows large bronchi which are filled with purulent exudate. Bronchi are lined with ciliated columnar epithelium. Bronchial walls contain no cartilage and only a slight amount of smooth muscle, which is very irregularly distributed. Some focal ulcerations of the mucosa are present. The pleura of the posterior surface of the lobe is present in the lower left-hand quadrant.

FIG. 113. (× 4) Boy, seven years of age. Case discussed in text. Section from lower portion of lobe. The numerous bronchi have thick connective tissue walls, little or no smooth muscle and cartilage, and are all lined with columnar ciliated epithelium. Some of the bronchi show some lymphocytic infiltration of the mucosa, but no ulcerations were found. The numerous blue areas are lymph node structures. There is a distinct paucity of lung parenchyma. No pleural adhesions were noted. Illustration is typical of structure of entire lobe.

FIG. 114. (× 4) Boy, nine years of age. Case discussed in text. Section through anterior portion of upper and middle lobes. The middle lobe is completely airless, but has an abundant alveolar structure. The area to the left in the upper lobe, which is suggestive of parenchymal scarring, shows, on higher magnification, an area of poorly developed lung and the presence of a considerable amount of smooth muscle. This latter finding definitely rules out scar formation. Note the absence of fissure between the lobes and the absence of any significantly large bronchi.

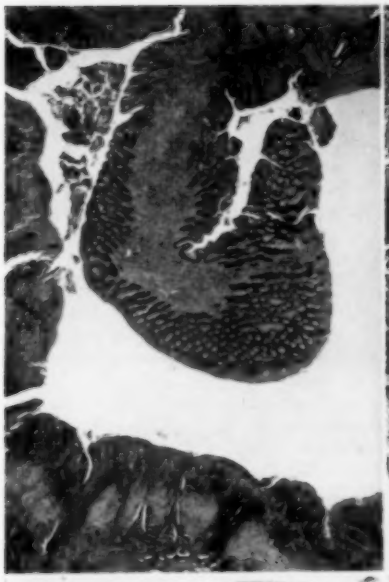


Fig. 111

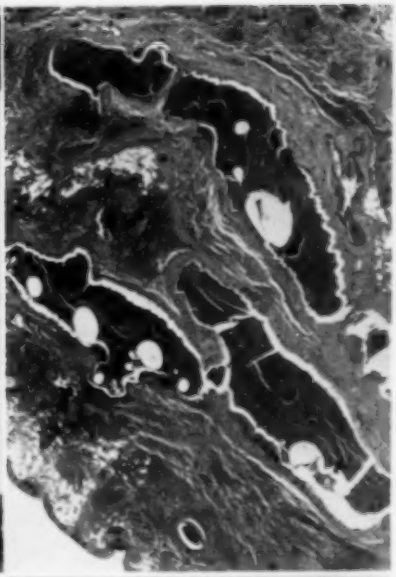


Fig. 112

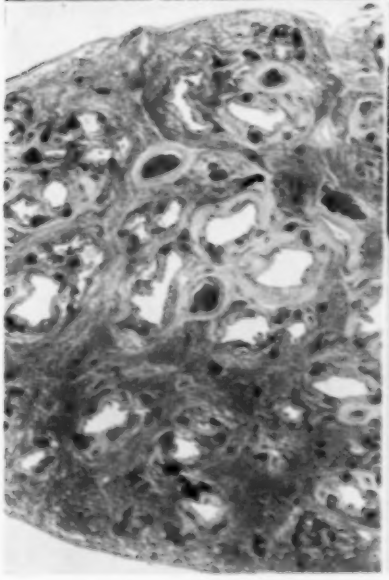


Fig. 113

Fig. 114

PLATE XXXVI

PLATE XXXVII

FIG. 115. (× 2) Negro female, twenty-five years of age. Case discussed in text. Illustration shows cystic bronchi which are lined with columnar ciliated epithelium. Tuberculous lesions are numerous in parenchyma, but there is little evidence of infection of cysts. The bronchiectatic condition was limited to the apical region of the left upper lobe. Note the absence of pleural adhesions.

FIG. 116. (× 3) Male Negro, thirty years of age. Case discussed in text. Section across the apical portion of the upper lobe. The large irregular open tuberculous cavity is in the left upper quadrant. To the right of the cavity and in the left lower quadrant, the large cystic bronchi show considerable necrotic endobronchial disease. The areas in which there is no necrosis have a ciliated columnar epithelial lining. In the left lower quadrant there is also considerable parenchymal scarring which represents healed non-necrotic tuberculous pneumonic lesions. In the right third of the illustration, note the large amount of connective tissue of normal structure, the numerous bronchi and blood vessels, and the considerable amount of cartilage. This area extends out to the pleura of the apical region. No evidence of tuberculosis was found in this portion of the tissue.

FIG. 117. (× 3) Same case shown in figure 116. Section from lower half of lower lobe. The large cystic bronchi are devoid of cartilage, have little smooth muscle, and are lined with ciliated columnar epithelium. The large bronchus in the lower right-hand corner shows a necrotic ulcerated area in the mucosa to the left. There is some parenchymal scarring of healed non-necrotic tuberculosis. The connective tissue which forms the walls of the large bronchi is of normal structure. Note the moderately large blood vessels within the broad bands of connective tissue. The cavity in the lower lobe was due to cystic bronchiectasis rather than to tuberculosis, as noted in the upper lobe.

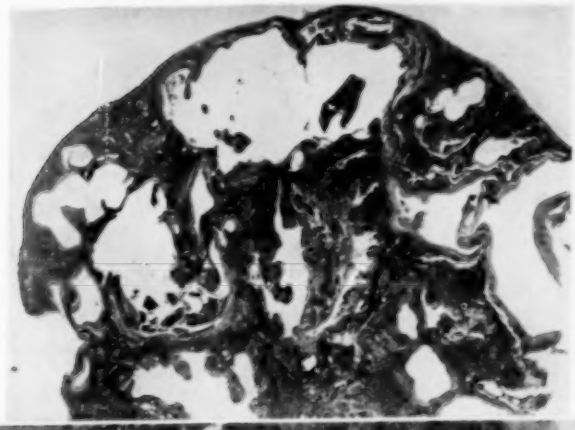


FIG. 115

FIG. 116

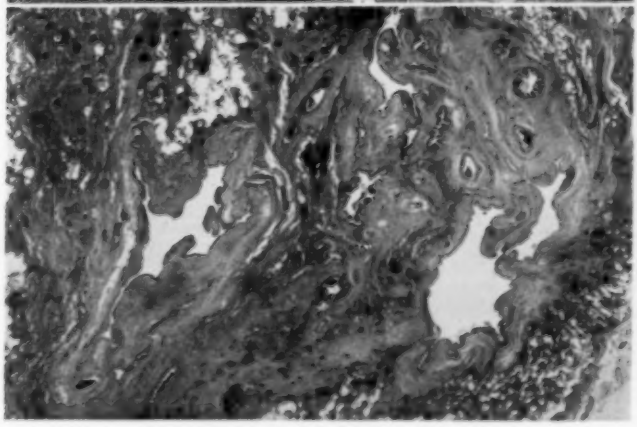


FIG. 117

PLATE XXXVII

PLATE XXXVIII

FIG. 118. (× 10) An ectatic bronchus with extensive ulceration and profuse production of granulation tissue. In the upper left quadrant there is a lining of ciliated columnar epithelium, and little inflammatory reaction is found in the mucosa. No evidence of tubercles, giant cells, or of necrosis which is characteristic of tuberculosis is present. Culture of the creamy pus from the lumen yielded a growth of pneumococci and was negative for tubercle bacilli. Other portions of the specimen showed many tuberculous lesions.

FIG. 119. (× 15) Section of clean cyst mentioned in the text. The stratified squamous epithelial lining is suggestive of the esophagus. Note the absence of scar tissue beyond the cystic area. There is a moderate lymphocytic infiltration in some areas beneath the epithelial covering. No evidence of tuberculous infection was found in the limited area of bronchiectasis which was present in the specimen. Many tuberculous lesions were present in other portions.

FIG. 120. (× 15) White female, twenty-five years of age. Case discussed in text. Illustration shows two of several large bronchi which were found near the pleura over the posterior portion of the specimen. There was no evidence of tuberculous disease in this region. The bronchial lining is of ciliated columnar epithelium, and there is no cellular inflammatory reaction in the mucosa. There is an abundance of smooth muscle in the wall of the larger bronchus in the lower half to the right and none in the remainder of the bronchial wall. Numerous tuberculous lesions were present in other portions of the lobe.

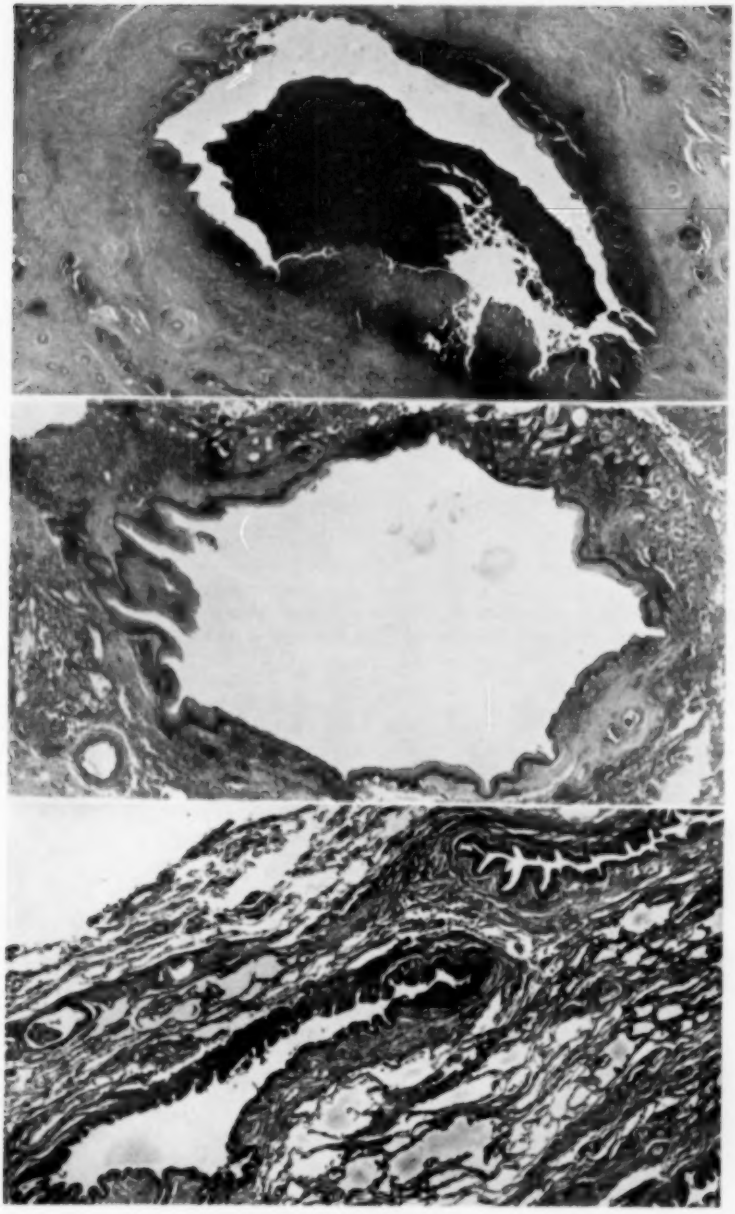


FIG. 118

FIG. 119

FIG. 120

PLATE XXXVIII

PLATE XXXIX

FIG. 121. (× 3) White female, eighteen years of age. Case discussed in text. Section from mid-portion of the lower lobe. In the upper right quadrant the large necrotic pneumonic tuberculous lesion communicates with a large cystic bronchus. In the lower left-hand quadrant the two long slitlike spaces are thin-walled cystic bronchi lined with ciliated columnar epithelium. These cystic bronchi contained no exudate and showed no inflammatory reaction in the mucosa. The upper and larger one contains some blood in its lumen. The bronchi were devoid of cartilage and smooth muscle. Note the several small parenchymal tuberculous lesions in the lower right-hand quadrant.

FIG. 122. (× 10) Section within 5 mm. of the diaphragmatic surface of the lower lobe. Three cysts at the top just beneath the pleura were filled with clear mucus under tension. The ciliated columnar epithelial lining is markedly flattened from pressure. These structures appeared to be bronchial cysts without any outside communication. In the lower portion, two ectatic bronchi were the seat of extensive necrotic tuberculous endobronchial disease. In the mid-portion, note the several moderately large bronchi and blood vessels. All of the bronchi in this region have a ciliated columnar epithelial lining and show at most only a light infiltration of lymphocytes in the mucosa. Their walls are devoid of both smooth muscle and cartilage.

FIG. 123. (× 10) White female, forty-two years of age. Case discussed in text. Section is from lower lobe and is within 1 cm. of the diaphragmatic pleura. All of the bronchi in the illustration show a superabundance of smooth muscle. There is a moderately large piece of cartilage in the upper right quadrant. There are only focal areas in which the mucosa is infiltrated with lymphocytes. The bronchi are lined with columnar epithelium which in some areas is ciliated, and in other areas the epithelial cells have the appearance of goblet cells of the gut. The magnification is too low to visualize this difference in the character of the epithelial cells. In many areas of the lobe the bronchi contain a considerable amount of mucoid secretion.

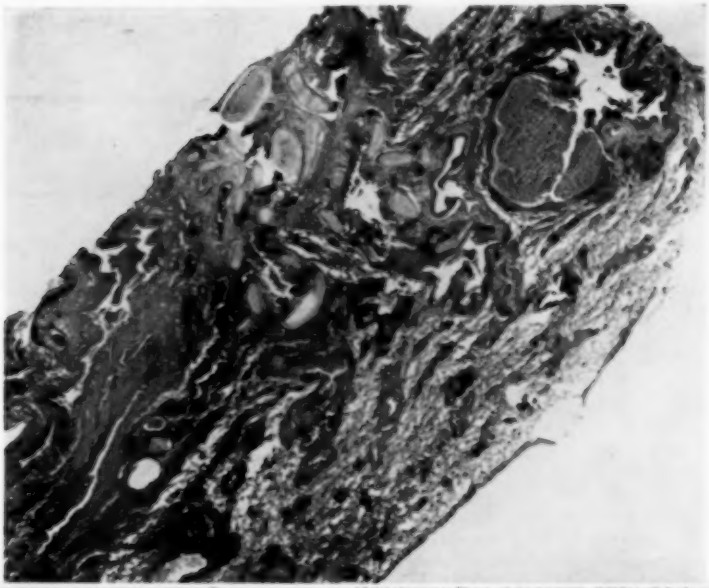


FIG. 121

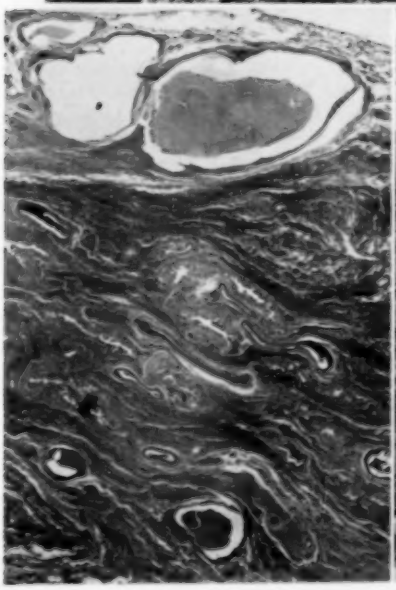


FIG. 122

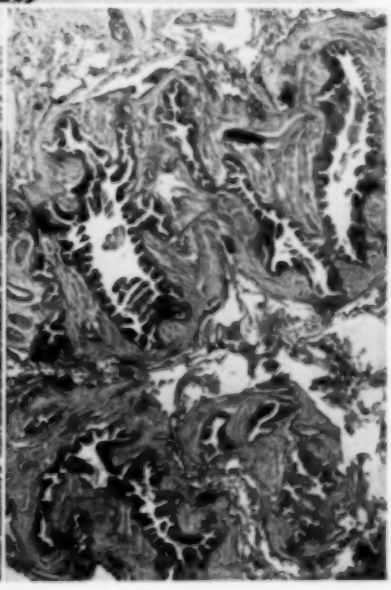


FIG. 123

PLATE XXXIX

PLATE XL

FIG. 124. (× 5) White male, forty-one years of age. Case discussed in text. Illustration is from the lower third of the lower lobe. The four large bronchial branches in the right half contain mucoid secretions in part and necrotic material in part. The two lower bronchi show extensive areas of necrosis which involve pieces of cartilage to the left. The large bronchus in the upper central portion shows a piece of free cartilage in the necrotic debris in its lower portion. Except for the areas of necrotic endobronchial disease, the bronchi are lined by ciliated columnar epithelium. Several necrotic parenchymal lesions are also present.

FIG. 125. (× 4) White male, twenty years of age. Case discussed in text. Illustration is from superior portion of the posterior segment. Two large bronchi in the central part have linings of ciliated columnar epithelium. The walls vary considerably in thickness and are composed in large part of connective tissue. Smooth muscle is sparse in amount, and no cartilage is present. There is no evidence of inflammatory reaction in the mucosa, and the bronchi were empty. In the upper right quadrant there is a cystic space with a wall similar to the bronchial walls, but there is no epithelial lining; there is also no evidence of inflammatory cellular reaction. In another section from the lobe a bronchus was found which connected by a large opening with a space of similar nature. In this instance the bronchial epithelial lining was normal up to the beginning of the unlined space. The writer has seen, on occasion, similar spaces without epithelial lining in cases of bronchiectasis.

Note the several blood vessels of moderate size, all of which had normal structure. Note also the broad bands of connective tissue. These would seem to be unusually large interlobular septa. No anthracotic pigment was present in these structures.

There was a considerable amount of parenchymal scarring in the lobe, and in such areas anthracotic pigment was present. The scarred areas were consistent with an organized lobular pneumonic process. In the illustration the parenchymal scarring is most evident in the upper left-hand quadrant below and to the left of the large bronchus. The several small blue spots are collections of lymphocytes. The apical pleura is shown on the extreme left. The parenchymal scars were the only suggestive evidence of a tuberculous process in the area shown. However, several small necrotic parenchymal tuberculous lesions were present in other areas of the lobe. One section showed a focal necrotic ulcerated area in one of the cystic spaces that had no epithelial lining.

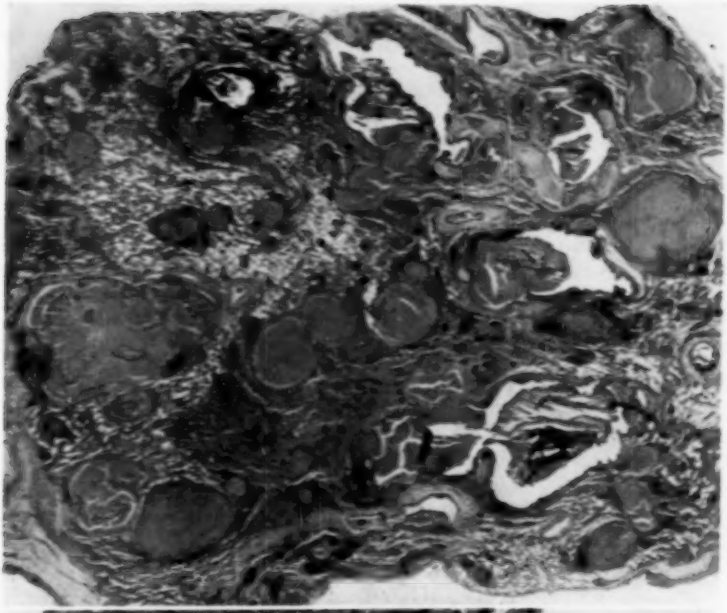


FIG. 124

FIG. 125

PLATE XL

CHAPTER IX

BACTERIOLOGIC OBSERVATIONS

The data and discussions presented in the previous chapters have dealt primarily with the variety of morphologic features of pulmonary tuberculosis. As these features are in large part the reactions of the host to the presence of tubercle bacilli, it is evident that the behavior of this parasite is of paramount importance. Throughout these investigations, the writer has been concerned primarily with a study of the host-parasite relationship rather than with a study of the behavior of tubercle bacilli on artificial media. Although it is essential to determine the potentialities and the characteristics of this parasite under a variety of artificial environments, investigations of such a nature are beyond the scope of the present discussion. In the following pages some bacteriologic observations will be presented which have a bearing upon the host-parasite relationship.

In experimental studies it can be readily shown that, in a first infection, virulent tubercle bacilli will reproduce in considerable numbers during the period prior to the occurrence of necrosis of the lesion. However, after necrosis has occurred, the bacilli are lysed to such an extent that, at most, only a few organisms can be demonstrated in the necrotic area. Several months later, masses of bacilli, much more numerous than in the pre-necrotic lesion, may be found in some of the necrotic foci.

Although changes in the bacterial population during the evolution of the necrotic lesion cannot be demonstrated in human tuberculosis, it would seem reasonable to assume that they do occur. It can be shown, for instance, that some unsloughed necrotic lesions in man contain masses of bacilli, even in colony formation. If the same processes observed in experimental animals occur in man, then delayed sloughing of necrotic pulmonary lesions makes possible new endobronchial disseminations which may be richly laden with bacilli which have reproduced after necrosis has occurred. This possibility constitutes a real threat to the tuberculous patient who has regained a state of clinical health. The writer admits ignorance of the nature of the forces at work in the host-parasite relationship during and subsequent to the phenomenon of necrosis.

Up to the present time the factors responsible for the virulence of tubercle bacilli have eluded analysis. Nevertheless, it would seem pertinent to record some observations on this subject. The test for pathogenicity of human tubercle bacilli requires recourse to an unnatural host. Even though this artifice may serve a useful purpose, it should be borne in mind that it still is an artifice which perhaps does not always reflect the natural host-parasite relationship.

The guinea pig is commonly used as the most vulnerable test animal for determining pathogenicity. On occasion a culture from a sputum containing nu-

merous organisms has all of the morphologic characteristics of human tubercle bacilli and yet may not be pathogenic for the guinea pig. At the other extreme, in an occasional sputum, tubercle bacilli which are too few to be found in smears and which do not produce colonies on artificial media will, on inoculation into a guinea pig, cause death within six weeks. Phenomena such as these are usually regarded as indicative of a variability in pathogenicity, and this interpretation may be correct. On the other hand, the patients referred to had evidenced progressive clinical disease from which they recovered clinically. It would seem that in these instances the natural host-parasite relationship might not be clearly reflected in the artificial host-parasite relationship. Proof of this possibility is lacking, for the natural host can hardly be used for the test.

Observations on cultures of tubercle bacilli suggest that the phenomenon of pathogenicity is changeable. An instance of this sort occurred when an incubator regulator stuck and the temperature rose to 45° C. for several hours during the night. All cultures in the incubator were transplanted the next day, and the only culture which survived was one of avian tubercle bacillus. The new growth from the transplant showed considerable pigment production, a feature which was lacking before. Inoculation of 10 mg. of this growth failed to produce a progressive disease in rabbits, whereas previously 0.01 mg. of bacilli would cause death in six to eight weeks. The culture was regularly transferred every three weeks and, after approximately six months, the chromogenicity disappeared. Coincidentally, animal inoculation showed that the organism had regained its virulence.

There are notable examples in which tubercle bacilli have lost their pathogenicity from long residence in an artificial environment. Perhaps the best known organism of this type is one of bovine origin (BCG) which has been used extensively for prophylactic vaccination against human tuberculosis. Twenty years ago, the writer and his associates, in carrying out an extensive study of this organism, sought to determine whether it could regain its pathogenicity in the course of repeated subcultures. The details of this study (4) have been published, and only a few pertinent remarks will be made here. The most significant feature was that, after many transfers on an enriched liquid medium, the culture began to grow out as a thin veil from the edge of the large central piled-up matted growth. From subcultures of this thin veil of growth, eventually a culture was obtained which grew only as a thin veil over the entire surface. Tests of this changed type of growth showed it was highly pathogenic for rabbits and guinea pigs and, hence, had the characteristics of a virulent bovine tubercle bacillus.

Following the introduction of chemotherapeutic agents in the treatment of tuberculous patients, a number of hitherto unsuspected capabilities of the tubercle bacillus have been observed. One such phenomenon is that, on occasion, tubercle bacilli may come to require the presence of considerable amounts of streptomycin in the medium to support growth. The writer and his assistants have studied one such culture. The bacilli were not pathogenic for guinea pigs even if the inoculated animals were given daily injections of streptomycin. By subculturing on media which contained less and less streptomycin, several isolated colonies eventually grew out on media which contained no streptomycin.

Subcultures of these single colonies showed that some were unable to grow in the presence of minute amounts of streptomycin, whereas others grew well on media which contained large amounts of the substance. All of the cultures caused progressive disease and death in guinea pigs. It would appear that pathogenicity was lost somewhere between the ability to grow in the presence of rather large amounts of streptomycin and the development of dependence on streptomycin to support growth.

These observations on pathogenicity are presented without an attempt to explain the observed phenomena. It would seem to be discreet to await further investigations of the factors involved. Perhaps with increased knowledge it may become possible to produce, at will, variants of various acid-fast bacilli with predetermined pathogenicity.

During most of the time the writer was engaged in his investigations, he also was in charge of routine laboratory work in a tuberculosis hospital. Such an arrangement has distinct advantages so long as time is available to pursue unsolved problems. In the early days a major feature of the laboratory routine was a monthly examination of direct smears of sputum from all tuberculous patients. Cultures for tubercle bacilli were usually not done. For diagnostic purposes, guinea pig inoculation was used to detect the presence of tubercle bacilli in sputum that failed to reveal organisms on microscopy. Thirty years ago it was considered a feat to obtain growth of tubercle bacilli on artificial media, and there was considerable controversy over the type of medium to use. During the same period of time "minimal" pulmonary tuberculosis was commonly considered to be a "closed" lesion.

To meet the problem of maintaining a staff of efficient and satisfied technicians, the writer made it a rule to combine, whenever possible, investigative work with the daily laboratory routine. Some of these investigations have been reported previously, and only brief comments will be made on the significance of some of the results.

The most onerous of all laboratory tests was the search for acid-fast bacilli in direct smears of sputum. Rather early in his experience as a director of a routine laboratory, the writer found that acid-fast bacilli were being found in the sputum specimens of only 15 per cent of the patients in the institution. As a control of the efficiency of direct sputum-smear technique, all sputum was digested and concentrated after direct smears were made. A smear, culture, and guinea pig inoculation of all concentrates of sputum were then made. In addition, fasting gastric contents were obtained from all patients who raised no sputum, and concentrates of the digested gastric contents were also examined by microscopy, culture, and guinea pig inoculation. This procedure (22) was carried out monthly for one year, and it was found that sometime during this period tubercle bacilli were found by culture or guinea pig inoculation in 85 per cent of the patients. Smears of sputum concentrates were somewhat superior to direct smear; cultures were distinctly superior to microscopy; and the guinea pig test yielded considerably more positive results than any other method. As a result of this study, the routine procedure was altered. All specimens of sputum and fast-

ing gastric contents were digested, and smears of concentrates were given only a brief examination. If they were negative for acid-fast bacilli, cultures and guinea pig inoculations were done. After a time examinations of smears of gastric concentrates were discontinued because so few were positive for acid-fast bacilli. In addition, the presence of acid-fast bacilli in smears of gastric contents was found to be unreliable as a diagnostic procedure for tubercle bacilli. It was found, moreover, that the pooling of fasting gastric contents obtained on two successive days gave optimum results for a routine procedure.

Although the guinea pig was found to be far superior to the culture media then in use for the detection of tubercle bacilli, the animal test was a rather expensive one. Search for a more satisfactory solid medium for routine cultures was then undertaken with the result that a medium (30) was obtained which was only slightly less efficient than the guinea pig test. With this finding, guinea pig testing was abandoned as a routine procedure and was reserved for special occasions.

Another study undertaken was the demonstration of tubercle bacilli in cases of "minimal" pulmonary tuberculosis (27). It was found that, with the use of proper material and technique and by repeated examinations, tubercle bacilli could be demonstrated in as high as 80 per cent of the patients with "minimal" disease. In this study it was found that the first specimen obtained upon hospitalization yielded the highest proportion of positive results. Even better was the examination of sputum or fasting gastric contents that were obtained before hospitalization was advised. At this time bed rest was the treatment of choice for the patients with "minimal" disease and, not infrequently, no tubercle bacilli could be demonstrated until the patients were placed on a regimen of graduated exercise.

The final bacteriologic study in this series of investigations, which were carried out at the Mt. McGregor Sanatorium of the Metropolitan Life Insurance Company, was a search for tubercle bacilli in a group of nontuberculous patients (29) who were housed in a separate building. The most significant findings in this study were the demonstration of pathogenic tubercle bacilli in sputum or fasting gastric contents in 1 per cent of the patients who had normal roentgenograms of the chest and in 15 per cent of a group of patients who had roentgenographic findings indicative of "healed" pulmonary tuberculosis.

During these studies, a number of rapidly growing cultures of chromogenic acid-fast bacilli were obtained, more often from gastric concentrates than from sputum. These organisms were nonpathogenic for the usual experimental animals and obviously were not tubercle bacilli. However, in 3 patients with abnormal shadows in the chest roentgenogram, chromogenic, nonpathogenic acid-fast bacilli were grown from sputum on several occasions. The writer at the time entertained the idea that these organisms might be of etiologic significance.

It is possible that organisms of the chromogenic, nonpathogenic, acid-fast type may be pathogenic for man but not for laboratory animals. This was indicated more recently by laboratory findings on a patient who had had a pulmonary lobe resected because of extensive roentgenographic shadows with evidence of cavity formation. The sputum of this patient showed numerous acid-fast bacilli repeatedly; and a yellow-colored, rapidly growing culture of acid-fast bacilli was

obtained on several occasions. Material taken from an open cavity in the resected specimen and from necrotic unsloughed pulmonary lesions gave a growth which was identical to that obtained from sputum. These cultures were not pathogenic for either the rabbit or the guinea pig. It seems probable that these so-called chromogenic, nonpathogenic, acid-fast bacilli may be pathogenic for man on occasion. In such cases the pathogenicity tests on laboratory animals fail to reveal the natural host-parasite relationship. Perhaps this situation is more frequent than is recognized at present.

BACTERIOLOGIC STUDY OF RESECTED SPECIMENS

The pulmonary tuberculous tissues which have been resected since the introduction of chemotherapy in the treatment of tuberculous patients afford an opportunity to study tuberculous disease both morphologically and bacteriologically at stages which hitherto have not been available. From the outset the writer has been interested in the bacteriology of these lesions, not only from the standpoint of a chemotherapeutic effect, but also with regard to the general problem of the numbers and distribution of bacilli in the lesions.

The first fifty specimens were not examined before fixation in 10 per cent formalin. These specimens were used to determine the variety of morphologic features which might be present in resected specimens. Open cavities, filled-in cavities, unsloughed necrotic lesions, and histologic tubercles with or without giant cells were found in one specimen or another. Random sections prepared from the specimens were stained by the Ziehl-Neelsen technique and were thoroughly searched for acid-fast bacilli. It was found that the distribution of bacilli, with respect to both numbers and location, was most erratic. Sections of cavity walls showed an irregular distribution of bacilli in the innermost portion and, not infrequently, the largest number of organisms were found in necrotic tissue in which no recognizable inflammatory cells were present. Frequently no bacilli were found in moderately large areas. Bacilli were seldom found beyond the zone of necrosis or of marked cellular inflammation, which usually was composed predominantly of neutrophils. The fibrotic tissue comprising the outer portion of cavity walls rarely showed any bacilli although, commonly, a considerable infiltration of lymphocytes was present; occasionally, histologic tubercles and giant cells were found.

One section of a filled-in cavity might contain large numbers of bacilli within the necrotic area, whereas a section taken at a different level might show no bacilli. This erratic distribution of organisms was also found in unsloughed necrotic lesions. In one unsloughed necrotic lesion, search for bacilli at twelve different levels from serial sections showed bacilli in only one level; and here there were large numbers in a localized area deep within the necrotic zone. Bacilli were rarely found in the outer portion of the fibrotic zones which surrounded filled-in cavities and unsloughed necrotic lesions. The size of a necrotic lesion was not necessarily a determining factor. Although bacilli usually were more easily found and were more numerous in larger lesions, they were most numerous in a small focus on occasion.

Numerous histologic tubercles and giant cells which were present in some

specimens were meticulously searched for bacilli. When on rare occasion a single acid-fast bacillus was found, invariably it was contained in an "epithelioid" cell. No bacilli were ever found in parenchymal scars, many of which were heavily infiltrated with lymphocytes.

From these observations it would appear that tubercle bacilli in appreciable numbers are to be found only well within necrotic lesions (Plate XLI) or near the inner surface of cavity walls. Even in these locations, the distribution is so erratic that failure to find organisms at one level does not exclude the possibility that large numbers are present at another level of the same lesion.

One of the features found in sloughing necrotic lesions and in the inner portion of open cavity walls was the predominance of neutrophils in the inflammatory cellular exudate. On many occasions unsloughed necrotic lesions showed focal areas which were heavily infiltrated with neutrophils and which bordered upon the encircling fibrotic zone. It was most unusual to find any tubercle bacilli in these areas.

Since the presence of neutrophils is commonly regarded as a reaction to bacteria other than the tubercle bacillus, it seemed advisable to determine whether secondary bacteria were present in the lesions found in resected specimens. The results (46) of the attempts to culture secondary organisms from resected lesions already have been published. Cultures from 23 open cavities, 33 filled-in cavities, and 38 unsloughed necrotic lesions failed to yield secondary organisms in a single instance. Evidently tuberculous lesions, even open cavities, seldom are secondarily infected. This finding proved to be of value in a subsequent attempt to grow tubercle bacilli from closed lesions, as it was now evident that organisms other than tubercle bacilli were absent from the material to be cultured.

A later study was concerned with a comparison of the bacillary content of necrotic tuberculous lesions, as found on microscopy, with results obtained from culture and guinea pig inoculation of material from the same lesions. A liberal amount of necrotic tissue from filled-in cavities and from unsloughed necrotic lesions was used in this study, as it was appreciated that bacilli usually were erratically distributed. For the same reason open cavities which contained little free material were extensively swabbed over their inner surfaces in order to obtain adequate samples. Entire small necrotic lesions were taken, and not infrequently pieces of lung which contained several small lesions were used. Each of the samples was homogenized in a sterile normal saline solution and the sediment used for smears, cultures and, in many instances, guinea pig inoculations. Care was exercised to utilize material from lesions which, macroscopically, seemed to be of different ages. As has been pointed out previously, it seemed apparent that many necrotic lesions long antedated the introduction of chemotherapy. For this reason the study was not conducted primarily to determine the effect of the chemotherapeutic agent on the bacterial population.

In a preliminary report (46), the results obtained from the study of 130 samples from 72 patients have been given. To this the writer adds the results obtained from 246 additional samples taken from 100 resected specimens which were removed from 73 patients. The combined data represent the results ob-

tained from the bacteriologic study of 376 samples taken from tuberculous tissue which was resected from 145 patients.

The results obtained from smear examination of the 376 samples showed that 25 per cent revealed no bacilli, 40 per cent contained few bacilli (Gaffky I), and bacilli were easily found, often in tremendous numbers, in 35 per cent. In the resected specimens in which only one lesion was examined, smears were negative for acid-fast bacilli in one-third; whereas, if three or more lesions were examined, bacilli were found in every specimen. The size of the lesion was not always a determining factor with regard to the number of bacilli, although bacilli were found more consistently in the larger lesions; whereas the small lesions yielded a higher percentage of negative results. Samples from 20 open cavities gave negative smears in three (15 per cent).

Cultures of these samples gave the following results: Of the 96 samples in which the smear was negative, growth of *M. tuberculosis* was obtained in 4 (4 per cent). Three of the positive cultures occurred in samples from open cavities and one from a piece of tissue which contained several small necrotic lesions. In the 280 samples which were positive for acid-fast bacilli on microscopy, growth of tubercle bacilli was obtained in 36 (13 per cent). Seventeen of the cultures were obtained from open cavities and 19 came from closed lesions. Growth of tubercle bacilli was obtained from each of the 20 open cavities sampled, with abundant growth in 16 and only a few colonies in 4. Only 20 (5 per cent) of the 356 solid lesions, filled-in cavities, and unsloughed necrotic lesions yielded growth of bacilli, and in no instance were more than a few colonies present. Although bacilli in large numbers were planted in one-third of the specimens, no more success was obtained in culturing tubercle bacilli from such samples than from those which contained few bacilli.

One specimen in the group was of particular interest. A large necrotic lesion which measured three centimeters in diameter had partially sloughed so that at one edge there was an open one-centimeter cavity. One sample was taken from the necrotic tissue which was in the cavity-bearing area, and a second sample was taken from the necrotic tissue which lay one centimeter away from the cavity. Smears showed large numbers of acid-fast bacilli in each sample. Culture of the sample from the area of cavity yielded abundant growth, whereas culture of the other sample yielded only a single colony.

Among the specimens were seven which had been removed from patients who had received only a few days of chemotherapy prior to surgery. Acid-fast bacilli were numerous in four, scant in two, and none were found in one. Cultures were negative for tubercle bacilli in each instance.

Three necropsy specimens are of interest with regard to the bacteriologic findings in tuberculous cases. In one, the patient had been known to have had a large filled-in cavity for approximately five years. At necropsy a five-centimeter lesion was found which was filled with putty-like material. Samples taken from four different areas showed numerous acid-fast bacilli in each, and cultures for tubercle bacilli were all negative. This patient had never had any chemotherapy.

The second patient had had a thoracoplasty twelve years prior to death. Ex-

tensive cavitary disease developed in the opposite lung and, although prolonged chemotherapy was given, the cavities failed to close. Of particular interest was a two-centimeter old filled-in cavity under the thoracoplasty. A sample of this material showed a fair number of well-staining acid-fast bacilli which failed to grow on artificial media.

The third patient was given streptomycin-PAS because of a three-centimeter cavity in the superior segment of a lower lobe and quite extensive parenchymal roentgenographic shadows below the cavity-bearing area. In approximately two months the cavity closed, and the sputum from that time on was negative for tubercle bacilli by microscopy and culture. Chemotherapy was continued uninterruptedly for eighteen months and the patient was kept in the hospital for two months after chemotherapy was stopped. By that time all sputum smears and cultures had been repeatedly negative for tubercle bacilli for an eighteen-month period. Approximately three months after the patient was discharged from the hospital, the cavity reopened and the sputum showed numerous acid-fast bacilli which grew readily on culture. Drug-susceptibility study of the cultures showed that the organisms would not grow in the presence of a small quantity of either streptomycin or PAS.

Guinea pig inoculation of the untreated samples was performed in 81 of the first 130 specimens which were studied. In no instance did the guinea pig show evidence of progressive disease if culture of the sample failed to produce growth of tubercle bacilli. On the other hand, in every instance in which a growth was obtained, the cultures were found to be pathogenic for the guinea pig. In the light of these results, further guinea pig testing of the samples from resected specimens appeared to be an unnecessary procedure.

Among the patients included in this study are 5 which had had sputum negative for tubercle bacilli for a considerable time prior to surgery and who showed bacilli in the sputum some time after surgery. Bacilli were demonstrated in the resected lesions in each case, and no growth was obtained on culture. In each case, several months following surgery and after chemotherapy had been discontinued, the sputum became positive and culture yielded tubercle bacilli which were pathogenic for guinea pigs.

In 3 of the 5 cases, the writer has had the opportunity to study the specimens resected after the clinical relapse had occurred. In each case the surgeon recorded that all palpable disease was removed at the first operation. Chemotherapy had been stopped within two months after surgery in each case because of the development of drug intolerance. Easily recognizable disease was found in each instance in the same general area of the lung from which the original disease was removed. In two of the three specimens from the second resection, surgical sutures were found in close association with some of the lesions. In all 3 cases several necrotic lesions were easily palpated in the second resected specimen, lesions which would not have escaped notice at the first operation. Necrotic debris was found within bronchi on microscopic study in all three original resected specimens.

All of these pathologic findings suggest the possibility that necrotic debris may have been dispersed during the first resection and that this material probably was the source from which the new disease had its origin. Since bacilli which

failed to grow on culture were demonstrated in smears from the first resected specimens, the obtaining of growth of pathogenic bacilli from sputum several months after chemotherapy was stopped presents a most intriguing bacteriologic problem.

GENERAL COMMENT

The foregoing observations indicate that the host-parasite relationship and the behavior of the parasite are subtle and varied. A satisfactory explanation of the observed phenomena is not available from the fragmentary knowledge which is at hand.

Consider, for example, the subject of pathogenicity. Although the tubercle bacillus can lose and then regain its pathogenic properties in an artificial environment, the factors concerned in these phenomena are not known. The bacillus may be pathogenic for a natural host and it may or may not be so for an unnatural host. The infection in one patient may proceed uninterruptedly to death, whereas in another a chronic sluggish disease may develop which may not even be incapacitating. Are such differences due to a difference in the pathogenicity of the parasite or to a difference in the inherent resistance of the patient? As neither the factors which determine the pathogenicity of the parasite nor those which are responsible for host resistance are known, there is an understandable inability to interpret the various phenomena which have been observed.

Modern techniques have made it possible to use with considerable success the culture method as a routine diagnostic procedure. These techniques, however, in the writer's opinion, are not an infallible test of the viability of the tubercle bacilli. Without doubt, tubercle bacilli are affected by the methods which are necessary in the preparation of diagnostic specimens because it is necessary to utilize techniques which will dispose of secondary bacteria. The tubercle bacillus is not a difficult organism to kill, and it is a most fortunate circumstance that some bacilli survive the rigorous treatment administered to them in the manipulations of diagnostic specimens. In general, in the preparation of diagnostic specimens, the exposure of tubercle bacilli to either acid or alkali should be reduced to an unavoidable minimum.

However, this is not the whole story. On occasion the writer has observed the growth of many colonies from concentrates which, after prolonged search, failed to show bacilli in smears. On the other hand, on occasion, only a few colonies of tubercle bacilli have grown from a concentrate which showed numerous bacilli in smears. These variations have been noted in diagnostic specimens which have been handled in an identical manner.

Specimens which contain numerous bacilli commonly show numerous visible colonies in two to three weeks after planting. On the other hand, specimens which contain few bacilli may not show visible growth within three months, and then only one or two colonies may appear. In the latter instance, the number of bacilli seem to increase rapidly after growth is established for, not infrequently, a colony in one week may increase from a pinpoint to two or three millimeters in diameter.

From these observations it seems unlikely that all bacilli are killed in one

specimen and not in another when the same technique is employed. Rather, it appears likely that all viable bacilli in diagnostic specimens are not capable of reproducing on the artificial media now in use. To assume that, because some bacilli are capable of reproducing in an artificial environment, all viable bacilli are capable of doing likewise would seem, to the writer, to be an unwarranted assumption. The life processes of the tubercle bacillus are little understood. The Koch bacillus still remains one of the more difficult bacteria to grow from sputum or other specimens.

Not infrequently tubercle bacilli cannot be demonstrated in sputum from patients with clinically active minimal or moderately advanced disease. On occasion an increase may appear in the roentgenographic shadows without an appearance of bacilli in the sputum at the time. Failure to demonstrate bacilli is due quite often to failure to obtain adequate specimens and a sufficient number of specimens for study. On the other hand, from the pathologic nature of the disease it is possible that the necrotic debris which has sloughed locally into a bronchus may all be dispersed within the lung rather than discharged to the exterior in the sputum. Several of the resected specimens included in this study came from patients in whose sputum and gastric contents bacilli were never demonstrated. In each instance multiple lesions, as well as bacilli, were demonstrated.

One of the goals in the treatment of tuberculous patients is to rid the sputum of tubercle bacilli. Evidence of cavity formation in the lung is of great concern, for it is now generally recognized that usually it is not possible to obtain a sputum negative for tubercle bacilli so long as evidence of cavity persists. Disappearance of bacilli from sputum is commonly called sputum "conversion" and frequently is regarded as a major indication of the effectiveness of clinical management. Not until the resection of tuberculous pulmonary disease has it been possible to determine the bacteriology of actual lesions and to compare the findings with sputum determinations.

Among the resected specimens which the writer has studied, there were only twenty in which open cavity was present; and in each case the sputum contained acid-fast bacilli prior to operation. No open lesions were found in the remaining specimens, and only in a rare instance had the sputum shown bacilli up to the time of operation. In the large majority of patients the sputum had been negative for tubercle bacilli for a considerable time preoperatively.

Although one-fourth of the individual, closed lesions which were tested failed to show bacilli, there were numerous bacilli in approximately one-third. Furthermore, in those specimens from which two or more lesions were examined, tubercle bacilli were found in every instance. From these observations one may conclude that the disappearance of bacilli from sputum is not a true indicator with regard to the numbers of bacilli which may be harbored within the persisting necrotic foci. Should these lesions again begin to slough, the likelihood of the appearance of tubercle bacilli in the sputum will be high. "Conversion" of sputum has great significance epidemiologically only so long as it remains converted. "Conversion" of sputum is also favorable for the patient. It would be most unfortunate, how-

ever, to regard a disappearance of bacilli from the sputum either as evidence of an eradication of the infection or as an indication that relapses of the disease may not occur.

The foregoing remarks have dealt with the bacteriologic problem in general. Naturally, in the resected tissues and in other specimens, one is concerned with the demonstrable effect of the chemotherapeutic regimens which have been used. It would seem advisable, however, to recall the observations made prior to the clinical use of chemotherapeutic agents in tuberculosis. The present discussion deals with personal observations which have been limited in large measure to examination of sputum and of resected tuberculous lesions. Here the main interest has been with the natural host-parasite relationship which may not be identical with conditions in an unnatural host or in the environment of the test tube. This does not lessen the importance of studies conducted under unnatural environments as a means of obtaining data relative to the host-parasite relationship.

There can be no question of the beneficial effect of certain chemotherapeutic agents. Also there is little reason to doubt that these agents reach the sites where the bacilli reside. This is clearly shown (47) by the fact that, not infrequently, cultures obtained from material within cavities and from unsloughed necrotic foci grow in the presence of considerable amounts of the chemotherapeutic agents which have been used. It is now recognized that changes in the ability of tubercle bacilli to grow in the presence of a chemotherapeutic agent are determined by several factors. Changes occur more readily and perhaps more often in bacilli which are present either in sputum or in open cavities than in closed lesions. Changes are affected by the amount of drug used and the length of time it is used. The concurrent administration of two agents at least delays any significant change in the growth characteristics of the bacilli.

Cultures of sputum obtained from patients who are receiving chemotherapy show considerable variation in the growth of tubercle bacilli on media containing the drug. During the era when chemotherapeutic agents were used singly, there were occasions when the organism developed, rather promptly, the ability to grow in a rather large concentration of the therapeutic agent. In some other instances, however, the bacilli evidenced little ability to grow in the presence of small amounts of the drug although it had been used for several months. With the use of multiple-drug therapy, the bacilli frequently develop the ability to grow in the presence of moderate concentrations of both drugs in patients whose cavitary lesions fail to close. On the other hand, the writer has observed one instance in which the bacilli were unable to grow in the presence of minute amounts of the agents even after eighteen months of multiple-drug therapy. These variations suggest that, although the bacilli are affected by certain antimicrobial agents, their response to the drugs is far from uniform. To the writer the reasons for the observed phenomena and their significance remain in a confused and unanswered state.

Undoubtedly the most important feature of the bacteriologic study of resected specimens is the inability to obtain growth of tubercle bacilli on artificial media

or to produce disease in guinea pigs in a high percentage of closed lesions. This situation is not directly related to the number of bacilli present in the lesions, for on many occasions entirely negative results have been obtained when masses of bacilli were inoculated. One outstanding feature in the writer's experience was that growth was obtained from every open cavity regardless of the duration of chemotherapy. For example, in a case in which drug treatment had been administered for three years, growth of virulent tubercle bacilli was obtained from the resected open cavities.

A quite different result was obtained in the study of samples from both filled-in cavities and unsloughed necrotic lesions. Here, growth was obtained in only 5 per cent of the lesions tested, and all of the cultures were pathogenic for guinea pigs. These results can hardly be claimed to be due in every instance to the effect of the chemotherapeutic agents, since seven of the lesions tested were obtained from patients who had received either no chemotherapy or at most only a few days of chemotherapy prior to surgery. Furthermore, the difficulty of obtaining growth from necrotic lesions was appreciated long before the era of chemotherapy.

As the bacilli found in closed lesions usually do not grow and do not produce disease in the guinea pig, it is tempting to assume that these organisms, although sometimes present in tremendous numbers, are dead. In this connection it is well to bear in mind that on occasion patients who have recovered clinically and who show no bacilli in their sputum have a relapse of disease years later. The finding of tubercle bacilli in a high percentage of filled-in cavities and of unsloughed necrotic lesions in the resected specimens suggests the source of the bacilli should a relapse occur. Apparently tubercle bacilli can remain alive within necrotic lesions for years, and the inability to grow these organisms directly from these lesions need not necessarily indicate that the organisms are dead.

Failure to demonstrate bacilli in one-fourth of the lesions examined suggests that complete destruction by lysis can occur quite often. On the other hand, the finding of masses of bacilli, often in colony formation, in some necrotic foci indicates that the bacilli which are not killed and lysed at the time of necrosis may multiply within the necrotic debris. It may be that the changes in life processes required to enable the surviving bacilli to multiply have rendered them incapable of reproducing readily on the media now in use. It would seem that the status of the bacilli in the residual necrotic lesions can hardly be determined by accepted techniques. Probably unorthodox procedures will be required to reach a solution of this problem. Under these circumstances, it would seem best at this time not to attempt to discuss the possible effect of chemotherapeutic agents upon tubercle bacilli which are harbored within necrotic lesions.

PLATE XLI follows

PLATE XLI

FIG. 126. (× 4) Illustration shows an actively sloughing necrotic parenchymal focus. The intense blue color is due to masses of neutrophils. Note that the necrotic tissue is being liquefied from the periphery. The central blue area in which there are a few clear spaces is interpreted as the region of the bronchus. Tubercle bacilli were present in the acute inflammatory cellular reaction, but they were not numerous. The sputum in this case was positive for tubercle bacilli by culture but not on smear at the time of surgery.

FIG. 127. (× 15) Higher power of the central blue area shown in figure 126. Acid-fast stain. The small red dots around the lower portion of the blue area, especially in the lower left-hand quadrant, are colonies of tubercle bacilli in undigested necrotic tissue. No bacilli were present in the other portion of the necrotic tissue. It seems obvious to the writer that these bacilli have multiplied subsequent to necrosis of the tissue.

FIG. 128. (× 15) Acid-fast stain. The red areas in the central portion of the illustration are masses of tubercle bacilli in areas in which the dead framework of lung parenchyma is intact. The necrotic lesion measured 1 cm. across, and bacilli were only found deep in the necrotic tissue. This lesion is undergoing liquefaction, and neutrophils were present in large numbers in some portions. In those regions bacilli were not found. The tuberculous disease was in the upper and posterior portions of the left upper lobe and consisted of a number of necrotic lesions. The tuberculosis was an incidental finding at necropsy on a patient who died from carcinoma. Specimen obtained through the courtesy of Dr. Ferrera, Vermont Medical School, Burlington, Vermont.

FIG. 129. (× 15) Acid-fast stain. The dark purplish red areas, largest in the right central part of the illustration, are masses of tubercle bacilli. The brownish black pigment is anthracotic pigment. The red streak in the right central area is blood. The illustration is from a solid, flexible, solitary necrotic lesion which measured 2.5 by 5 cm. on cross-section. Some small foci of calcification were found, and there was little evidence of liquefaction of the necrotic pneumonia. Masses of bacilli were found in a few focal areas deep within the necrotic tissue, whereas no bacilli were present in large areas. The masses of bacilli would seem to represent multiplication of bacilli which had survived the process of necrosis. Specimen obtained through the courtesy of Dr. Marvin Kushner, Pathologist, First Division, Bellevue Hospital, New York City.

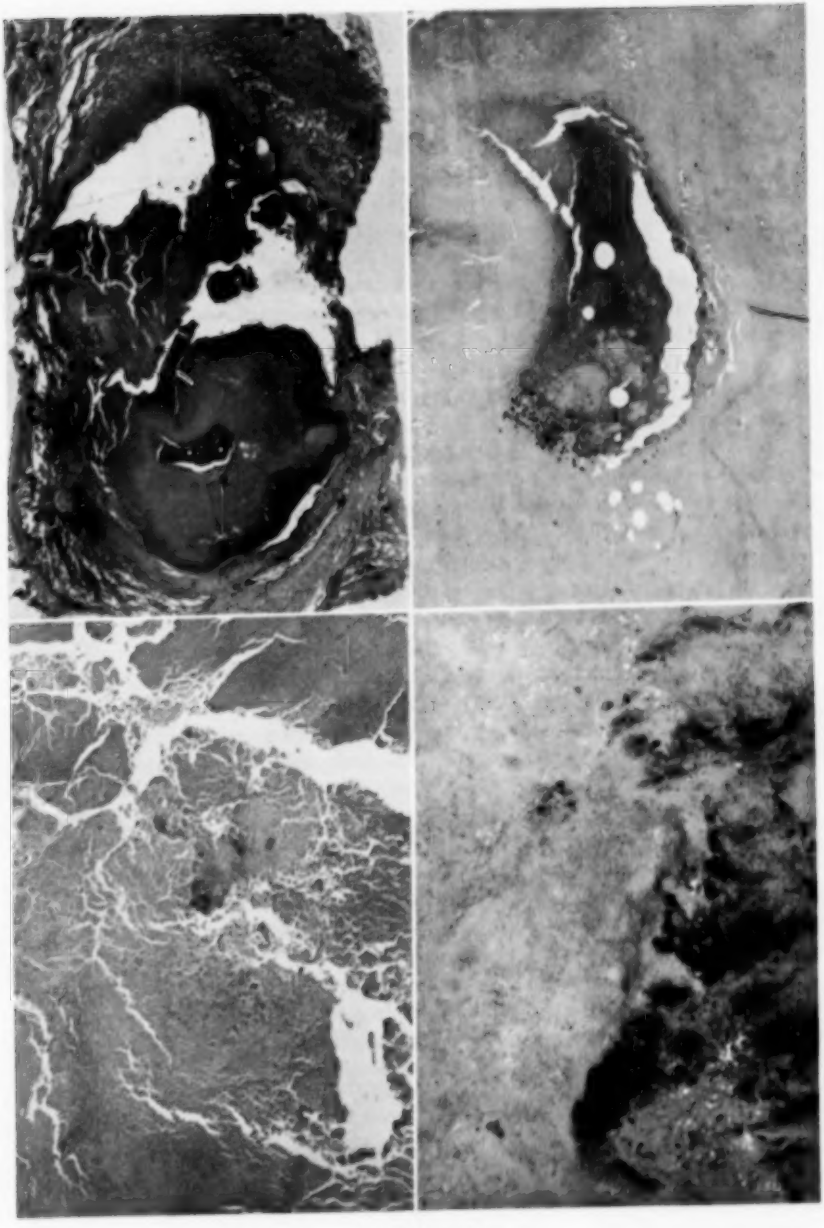


Fig. 126

Fig. 127

Fig. 128

Fig. 129

PLATE XLI

CHAPTER X

RE-EXAMINATION OF THE PROBLEM

Throughout these investigations of tuberculosis, the writer has been concerned primarily with the interaction between the human host and the infectious agent. In these studies a broad perspective of the problem was sought. The main theme has been a study of pulmonary tuberculosis, for infection of the lung in man represents the major problem. It appeared essential to determine the sequence of the events in the observed morphologic changes which begins with the initial infection and terminates with either the death of the host or complete eradication of the infectious agent. Suitable material for such a study cannot be obtained solely from human sources. Consequently, recourse to experimentally produced disease was used to obtain analogues of the essential human pulmonary lesions. The determination of the time-sequence of events in the development of the various experimental lesions has been of fundamental importance to the writer in his understanding of the considerable variety of lesions which are commonly found in human pulmonary tuberculosis.

During the past twenty-five years he has been a regular attendant at clinical conferences at which the problems of diagnosis of diseases of the chest and of management of tuberculous patients have been discussed. The reason for attending these conferences was to gain a better appreciation of the clinical problems in order that laboratory investigations could be directed toward a clarification of some of the perplexing situations. In the foregoing chapters, the data and the discussion have dealt with investigations which, to a large extent, have stemmed from questions that had arisen during clinical conferences. Perhaps the data obtained from the study of resected pulmonary disease will be of greatest interest to the practicing physician because the welfare of the patients from whom these specimens have been removed continues to be of real concern. The other data and discussions, however, form a necessary background for the consideration of the problem as a whole.

From the data which have been presented, it seems appropriate to re-examine the problem which was presented at the beginning. If in this re-examination the writer departs from the concepts he was taught, it is because the accumulated evidence has altered his understanding of the disease.

BEHAVIOR OF PULMONARY LESIONS

The data affirm the accepted concept that pulmonary tuberculosis is, with perhaps rare exceptions, an air-borne infection which is initiated by inhalation of minute tubercle-bacilli–containing particles. No evidence was found which would support the notion that a massive pulmonary disease can develop promptly from an air-borne infection. Evidence was obtained which indicated that mul-

tiple minute and widely scattered lesions could be caused by inhalation of polluted particles. These minute foci may be found in any portion of the lung parenchyma. The pattern of distribution suggests that the site at which the polluted particle lodges is purely a matter of chance. The data indicate that the minute initial lesions in the lower portions of pulmonary lobes seldom give rise to progressive disease. Commonly they undergo necrosis, and the small necrotic foci heal either by calcification or by hyalinization.

It was found in the experimental studies that under certain conditions the local inflammatory reaction would proceed to histologic tubercle formation which would heal and leave only a microscopic scar. Perhaps this may occur in local initial pulmonary lesions in man. However, it was not possible to obtain data to support such an assumption.

The evidence suggests that the initial small lesions which develop in the superior portions of pulmonary lobes often undergo necrosis, liquefaction, and sloughing into bronchi and in this manner give rise to a progressive pulmonary disease. On occasion, lesions in these locations may necrose without a subsequent liquefaction and sloughing. Under these circumstances the small focus heals completely, either by fibrosis or by a combination of fibrosis and calcification, and the infection does not become evident clinically.

Even though liquefaction and sloughing of an initial necrotic lesion occur, endobronchial dispersion of the slough may be limited to a small portion of a pulmonary segment. In some cases further extension of the disease may not ensue, and eventually complete healing may occur. Cases of this nature, if it were possible to follow them by serial roentgenograms of the chest from the development of a reaction to tuberculin, would reveal at some time clinically active "minimal" pulmonary tuberculosis which in time would recede to a variable amount of linear and more dense calcific roentgenographic shadows.

In other cases the disease may progress in a sluggish manner for a period of years, with some foci undergoing healing; while in others partial and intermittent sloughing makes possible new endobronchial disseminations. On occasion, the original minute focus has been found in a calcified state and in direct association with a moderately large necrotic focus which was being liquefied and sloughed. Under these conditions the unhealed disease may remain undemonstrable roentgenographically for a considerable period of time before a sufficient volume of lung tissue has become involved to cast a recognizable shadow. Patients in whom the disease behaves in this manner eventually may develop advanced pulmonary tuberculosis.

In still other cases, the liquefaction and sloughing into bronchi of the initial necrotic focus may lead to moderately large new foci of tuberculous lobular pneumonia fairly promptly, and these new lesions may repeat the same process in rather short order. It is probable that the disease process goes through the same sequence of events which produced a localized sluggish disease in other cases. However, because of the faster tempo of liquefaction and sloughing, the disease remains localized for only a short time before it involves moderately large and widely separated areas of lung parenchyma.

Although the division of pulmonary tuberculosis into stages of minimal, moderately advanced, and far advanced disease has no bearing on the duration of the pathologic process, it serves a useful clinical purpose by indicating roughly the extent of lung involvement. It appears from all available evidence that clinical pulmonary tuberculosis is always initiated by the liquefaction and sloughing of a minute lesion of necrotic lobular pneumonia which develops in "vulnerable" portions of lobes. The age and the extent of the disease when first recognized clinically is conditioned by the promptness with which secondary lesions undergo necrosis, liquefaction, and endobronchial sloughing; by the volume of the slough; and by the amount and the distribution of the sloughing debris which has been dispersed through bronchi to new areas of pulmonary parenchyma.

THE NON-NECROTIC AND NECROTIC COMPONENTS

It is evident from the examination of the resected specimens that clinically detectable tuberculosis is always a multiple-lesion affair. Data from necropsy study of individuals who died from causes other than tuberculosis reveal the same situation. As the multiplicity of lesions represents endobronchial disseminations, hence secondary lesions, it is essential to bear in mind that the lesions are induced by dispersed sloughing necrotic tissue in which the bacillary content often varies widely. Examination of the specimens shows that there are two major components in the disease process and that there is a wide variation in the proportion of the disease which is represented by each component. These two components may be designated, for ease of discussion, the non-necrotic and the necrotic lesion.

In the beginning, the non-necrotic lesion consists of areas of lobular pneumonia in which the cellular exudate consists predominantly of lymphocytes and monocytes (epithelioid cells). Lesions of this nature may behave in one of two ways. Complete resolution may occur, and an intact lung framework be left. Pneumonic lesions which behave in this manner may be considered to represent a reaction to dispersed necrotic debris, a sort of chemical pneumonia, in which bacilli were either absent or were present in extremely small numbers.

On the other hand, an extensive formation of histologic (monocytic) tubercles may develop. To a variable degree these structures may show a small necrotic central portion, and giant cells are sometimes numerous. It appears that the necrotic centers occur in regions where small numbers of bacilli were present in the dispersed sloughing debris. Bacilli are always difficult to demonstrate in lesions of this nature but, if a sufficient number are searched, an occasional bacillus may be found. The writer has not found evidence to indicate that bacilli multiply to large numbers in these areas. Moreover, no evidence was found to support the idea that the lesions increase much in size or that they undergo further necrosis after they are once formed. Giant-cell formations usually are associated with the lesions which have a small necrotic area. It appears that these structures are foreign-body giant cells, the foreign body in this instance being the necrotic tissue. These histologic tubercles eventually heal completely by scar formation although, not infrequently, complete healing requires a lapse of con-

siderable time. This would seem to be the component which accounts for most of the parenchymal scarring not directly associated with cavity walls.

It is probable that in most instances non-necrotic lesions heal both by resolution and by scar formation, each process occurring in a variable degree. The scars would represent healed tubercles. It would appear from all of the evidence at hand that the disappearance of roentgenographic shadows represents in large measure the healing of the non-necrotic component of the tuberculous disease.

The necrotic (caseous) component consists of areas of tuberculous lobular pneumonia which have undergone necrosis. The framework of dead lung tissue is present and is intact prior to liquefaction. However, with liquefaction, the lung architecture becomes comminuted to a considerable degree, and thus sloughing of the lesion becomes possible. If moderately large liquefied areas are sloughed, then demonstrable cavity formation occurs. Not infrequently portions of intact dead lung tissue may be found in the inner portion of a cavity wall. Thus, with cavity formation, fragments of the necrotic lung tissue which have not been liquefied often remain and, hence, cannot be sloughed. Should cavities of this nature become closed, then the central necrotic area would be devoid of any lung structure.

Usually the necrotic (caseous) lesion which is found in human pulmonary tuberculosis shows a well-formed peripheral fibrotic zone or capsule. It is evident that these lesions are not of recent origin. Nevertheless, the writer has been unable to determine in the human disease the time-sequence of events in the formation of this encapsulated lesion. It has been necessary to use observations in experimentally produced tuberculosis to supply information relative to the sequence of events prior to encapsulation.

In the experimental animal, the lobular pneumonic lesion which eventually necroses is one in which neutrophils are the predominant cellular component and tubercle bacilli are abundant. In a first infection, there is no evidence of necrosis in such a lesion during an initial period of two to three weeks, although during this time bacilli have increased to large numbers. The first evidence of necrosis is found in the periphery of that portion which becomes completely necrotic in a subsequent period of two or three weeks. During this period there is no evidence of a delimiting fibrotic periphery. In necrotic lesions of several months' duration, however, an encircling zone of fibrous tissue is always present.

This time-sequence of events, which can be demonstrated readily in experimentally produced pulmonary tuberculosis, suggests that the encapsulated necrotic lesion in man is at least several months old and that, in all probability, the peripheral fibrotic zone was laid down subsequent to the occurrence of necrosis. Evidence to support the time-sequence of events observed in experimentally produced tuberculosis can sometimes be obtained in the study of lungs from persons who have died from the disease. However, there are two circumstances which cause the findings in man to be not entirely comparable to the observations in animals. First, nonencapsulated necrotic lesions are found only in pneumonic lesions which are the result of endobronchial dissemination in an allergic soil: whereas, in the animals, similar lesions are not endobronchial disseminations and have developed in a nonallergic soil. The second feature is that secondary

bacteria commonly can be demonstrated in the human lungs, and this perhaps may influence the process. Although the entire sequence of events which occurs in the formation of encapsulated necrotic lesions cannot readily be demonstrated in human tissues, it seems that an essential point in the understanding of this component is that necrosis can and probably does precede fibrotic encapsulation.

Once the zone of necrosis is delimited and a zone of fibrous tissue has been laid down around it, there is little evidence that any further enlargement of the lesion occurs. The only evidence suggesting that such lesions increase in size is necrosis of the peripheral fibrous tissue, a finding which occasionally can be demonstrated in a so-called "tuberculoma." The few lesions of this nature which the writer has had the opportunity to study have shown a laminated structure. Each layer was composed of necrotic fibrous tissue, and a layer of viable fibrous tissue surrounded the entire circumference. In these lesions there was no evidence of liquefaction of the dead tissue. Tubercle bacilli could not be demonstrated either in the encapsulating viable tissue or in the zones of dead fibrous tissue. The writer is unable to offer a satisfactory explanation for the development of such lesions.

It is remarkable that in most instances only a thin layer of fibrous tissue separates healthy lung tissue from the older necrotic tissue, even if lesions contain bacilli in large numbers. This situation suggests that in large measure the necrotic tissue per se is only mildly noxious. Two other observations support this opinion. The first is the resolution of non-necrotic lesions which represent seedings of necrotic debris in which few bacilli are present. The second is the frequent failure of bronchi which serve as drainage canals for sloughing lesions to show anything more than a chronic bronchitis.

Although the walled-off necrotic lesion has little effect on the contiguous lung tissue, four features make it a potential hazard to the patient. First, for some unknown reason, dead tuberculous tissue is most difficult to dispose of. Necrotic lesions only a millimeter or two in diameter when completely healed remain indefinitely as calcified or hyalinized foci. The larger the lesion, the less the likelihood that complete healing will occur.

The second feature is the bacillary content of the necrotic lesion. In resected specimens, lesions of this type frequently appear to be the only harborers of tubercle bacilli and quite often contain large numbers which may be found in limited and unpredictable areas. Attempts to grow these bacilli directly from the lesions and to produce progressive tuberculosis in guinea pigs have failed in a majority of cases. Naturally this raises the question of the viability of the bacilli. In this regard the known tendency for pulmonary tuberculosis to relapse years after recovery of clinical health needs careful consideration. To the writer, the most likely source of the bacilli in these relapses is the bacillary content of the necrotic lesion.

The third feature is the tendency of the necrotic lesions to liquefy and slough. As lesions of this type are areas of necrotic pneumonia, it is apparent that the dead lung framework would have to become disintegrated before sloughing to any extent could occur.

The study of the resected specimens shows clearly that neutrophils generally

are abundant in lesions that are sloughing. Also, focal neutrophilic infiltrations are frequently present in the necrotic tissue next to the fibrotic periphery. It appears that neutrophils are intimately associated with the process of liquefaction in tuberculous lesions as they are in other pathologic processes in which liquefaction of dead tissue is induced.

The areas which neutrophils invade often show no tubercle bacilli; conversely, the areas of necrotic tissue in which tubercle bacilli are present in masses often do not show a disintegration of the dead tissue. Thus, it would seem that the process of liquefaction is not directly related to the bacilli.

In some instances, only one of many necrotic lesions shows evidence of liquefaction; in others the majority of these lesions are liquefying; and, in others, little evidence of the process is found. Since cavity formation can take place only after the liquefaction and sloughing of considerable amounts of necrotic tissue, it would seem that this disintegrating process is the paramount feature of progressive tuberculosis.

It appears that here is a major problem which needs solution before it will become possible to eradicate the disease. If a way could be found to induce complete sloughing of all necrotic lesions under controlled conditions, i.e., under chemotherapy, or if a method could be discovered which would prevent the sloughing of any necrotic lesion, then pulmonary tuberculosis could be completely cured.

The fourth important feature of the necrotic lesion is the ever present communicating bronchus. Formerly it was assumed that the necrotic lesion was completely walled-off and that only the necrosis and rupture of the encapsulating fibrotic tissue into a bronchus enabled the escape of the necrotic debris with its bacillary content. The data presented earlier clearly show that the vulnerable point of the necrotic lesion is the patent connecting bronchus. It has been shown that the bronchial connection with a ten-millimeter necrotic lesion may be less than one-tenth of a millimeter in diameter. The only way to demonstrate this fact is to make and study *complete* serial sections because it is not possible to predict at what point the bronchial connection may be found. The evidence lends no support to the assumption that the connection between a bronchus and a necrotic lesion is formed only after necrosis and liquefaction of the fibrotic capsule have occurred.

BRONCHIAL LESIONS

The most common bronchial lesion is a chronic inflammation of the bronchi that drain sloughing parenchymal lesions. The cellular inflammatory reaction is predominantly lymphocytes. This is a reversible process and completely disappears once sloughing from parenchymal foci stops. The next most common lesion is histologic tubercle and giant-cell formation. These, in the opinion of the writer, represent an implantation of tuberculous infection. Lesions of this character commonly disappear once the process of sloughing is stopped. They rarely play any role in the production of necrotic ulcerative endobronchial disease. Necrotic endobronchial disease is less common and presents a problem that is analogous

to parenchymal cavity formation. It would seem to be induced by a stagnation of sloughing necrotic debris within bronchi.

The bronchus which leads into the necrotic pneumonic focus frequently shows a normal epithelial lining up to the juncture with the necrotic tissue. Usually necrotic debris juts into the lumen of the connecting bronchus. On the other hand, the bronchus may show a necrotic inner portion for a variable distance proximal to the lesion. Such bronchi commonly are filled with necrotic debris and apparently may remain in this condition indefinitely. If this occurs, there usually is an increase of fibrotic tissue peripherally, just as there is a similar process peripheral to the area of necrotic pneumonia. On the other hand, the necrotic area may become liquefied and slough. If this occurs, the cleansed surface may be covered by stratified squamous epithelium or, on infrequent occasions, the two clean surfaces may be joined and the bronchus become obliterated by scar tissue. More often only partial sloughing occurs and, with an increase of scar tissue, partial stenosis takes place.

It has not been found that the usual clinical type of bronchiectasis can be related directly to tuberculous infection of bronchi. Distension of bronchi due to retention of secretions beyond an area of bronchial stenosis or due to pressure from scar tissue has been observed on several occasions. This condition might be considered to be distention of bronchi distal to an obstruction rather than bronchiectasis. Bronchi so affected could hardly be visualized in bronchograms because of the obstruction and also because the bronchi already are filled with secretions. Bronchi may become foreshortened and tortuous due to extensive parenchymal scarring or to prolonged collapse under pneumothorax or thoracoplasty. Commonly these bronchi reveal no tuberculous infection. In such cases bronchographic studies may reveal an abnormal pattern. This situation is due to bronchial distortion rather than to bronchiectasis. Developmental bronchiectasis and tuberculosis may be associated but, in the opinion of the writer, they bear no etiologic relationship.

In the examination of the numerous resected specimens, it appeared that many of the smaller necrotic foci included limited segments of bronchi. It seems probable that lesions of this nature may be caused by the arrest of a plug of dispersed necrotic debris in the lumen of the smaller bronchial branches. It seems reasonable to anticipate that, in bronchograms, bronchi so affected would fill only to the point of the lesion and, as a result, some of the bronchi might give one the impression of dead limbs on a tree.

REINFECTION AND SUPERINFECTION

The term reinfection tuberculosis is one which is used commonly and loosely in clinical discussions. A brief discussion of the use of this term seems appropriate since considerable confusion has arisen as to its precise meaning. By definition, a reinfection is a new infection by the same microorganism. Should the use of this term be limited to an infection subsequent to complete healing of a previous infection or should its application be broadened to include new areas of disease that occur before the original infection has been eradicated? If the meaning of the

term is to be restricted to the first interpretation, then evidence must be produced to show that a previous infection has healed completely. If the definition is to be broadened to include any new area of disease, all tuberculous patients exhibit one reinfection after another, for by its nature tuberculosis is a metastasizing infection, be it through bronchi, lymphatics, or blood stream.

To clarify the sense in which the term reinfection is commonly used, the modifying terms endogenous and exogenous have come into use. A third term, superinfection, has been proposed to indicate that a person who harbors unhealed disease has contracted a new exogenous infection. All tuberculous patients have endogenous reinfections, if one chooses to retain this term. It would seem preferable to discard the term altogether and replace it by the use of the term focal endobronchial extension of disease. This would indicate that the person harbored smoldering unhealed disease.

If the term endogenous reinfection is discarded, obviously the modifying term exogenous is superfluous when the term reinfection is used. The writer has used the term reinfection consistently to denote a new infection in a person with morphologic evidence of a completely healed previous infection. The data which have been presented and discussed in the foregoing pages afford proof that reinfection tuberculosis is a reality of serious import and is found predominantly in persons more than forty years of age, particularly males.

The reality of superinfection in tuberculosis seems most difficult to prove, although the possibility must be admitted. There are three circumstances which must be considered in this situation. First, as has been repeatedly pointed out, unhealed necrotic lesions persist indefinitely in a tuberculous patient who has regained clinical health. The possibility that these lesions may undergo a long-delayed liquefaction and slough makes it appear that they are usually the source for relapses of the disease.

The second circumstance is that an air-borne tuberculous infection begins as a minute local focus of lobular pneumonia and that, by the time it can be recognized clinically, multiple lesions are present as a result of the liquefaction and sloughing through bronchi of the initial lesion. There is no morphologic evidence that the sequence of events which occurs in a first infection differs essentially from that which occurs either in a reinfection or in a superinfection. This makes the morphologic identification of a superinfection difficult, if not impossible.

The third circumstance is the occurrence within a limited area of lung of necrotic lesions which, on morphologic evidence, appear to be of different ages. If superinfections are assumed to occur in the portion of a lung that harbors unhealed disease, it would seem futile to attempt to distinguish between superinfection and other necrotic lesions on purely morphologic grounds. From the clinical behavior and the morphologic nature of pulmonary tuberculosis, it would seem that relapse of the disease could more reasonably be attributed to the liquefaction and sloughing of pre-existing necrotic lesions than to superinfection.

PRACTICAL IMPLICATIONS

The foregoing discussion is based upon morphologic findings in tissues which were obtained from persons who were, with individual exceptions, in a state of

good clinical well-being. The purpose of the discussion has been to indicate the dynamic nature of the pathologic process as well as the potentialities of unhealed tuberculosis which remains after a patient has regained a state of health. Perhaps this presentation may be of practical use to the physician in several ways. It indicates how a tuberculous infection becomes a clinical disease. The potentialities of residual disease may serve to focus attention on the need for proper management of tuberculous patients who have regained their clinical health. In young adults, there is a high probability that the individual has a progressive primary tuberculosis; hence, there is a greater hazard of hematogenous dissemination. Epidemiologically, the reality of reinfection tuberculosis predominantly in persons more than forty years of age indicates that no age group should be neglected in the search for new cases. A normal roentgenogram of the chest at the age of forty in no way precludes the possibility of finding progressive reinfection tuberculosis at a later date.

ALLERGY AND IMMUNITY

In no other infection has the influence of an allergic state engendered so much discussion as in tuberculosis. In the original sense the term allergy was used to denote a changed condition of the tissues of the host after an infection had occurred. Later there were attempts to separate the phenomenon of hypersensitivity to tuberculin from other phenomena of allergy which came to be regarded as indications of acquired resistance. One school of thought attributed a deleterious effect to the development of hypersensitivity to tuberculin, whereas another suggested that a beneficial effect resulted. Still later the state of hypersensitivity was subdivided into two phases: hyperergy and anergy. A primary tuberculous infection was considered to exist only until the phenomenon of hypersensitivity to tuberculin became manifest, and all manifestations of tuberculous disease after this date were labeled post-primary tuberculosis. An integral part of this theory was the idea that the pathology of the disease was greatly affected by the establishment of the state of hypersensitivity to tuberculin.

Then came the interpretation of the morphologic features of the disease on the basis of the state of hypersensitivity. The acute inflammatory response, the "exudative" phase of the disease, came to be regarded as a response to tuberculin. The breakdown of the fibrotic wall about a necrotic (caseous) lesion was attributed to a tuberculin reaction in the area. This breakdown in the fibrotic capsule through a bronchial wall permitted the extrusion of the necrotic (caseous) contents, and thus the formation of the tuberculous cavity was induced. The phenomenon of necrosis (caseation) came to be regarded as due to a hypersensitivity to tuberculin. Finally came the notion that histologic tubercle formation without necrosis represented an anergic phase of the pathology, and on this basis Boeck's sarcoid was thought to represent an anergic form of tuberculosis. These concepts are recorded to form a background for the writer to discuss his own observations on the relationship of allergy, as originally defined, to the morphologic features of pulmonary tuberculosis.

All human tuberculous lesions which become available for study are from persons who have long since become reactors to tuberculin. Commonly in these pa-

tients a multiplicity of lesions of different morphologic character are found. In some specimens of resected pulmonary tuberculous tissue, it is possible to demonstrate early lobular pneumonia which in some areas is composed in large part of lymphocytes and monocytes (epithelioid cells), whereas in other areas the predominant cell is the neutrophil; histologic tubercles in various stages of formation and of fibrotic organization; necrotic lesions that are sloughing; necrotic lesions with considerable infiltration of neutrophils and others with no evidence of neutrophilic infiltration; and parenchymal scars. In such specimens the writer has found no microorganisms other than the tubercle bacillus. To explain this complex morphologic picture on the basis of allergy, it would seem necessary to accept the idea that the factors of resistance, of hyperergy, and of anergy are involved in adjacent focal areas. Although this explanation may have an appeal, it is not supported by experimental proof.

The data on experimental studies presented in a previous chapter include observations on the phenomena of allergy. One such finding was that an experimental animal can become a reactor to tuberculin when infected with different types of tubercle bacilli, but shows a quite different morphologic reaction to each type. In one instance the reaction consisted predominantly of monocytes (epithelioid cells), and no necrotic lesions were formed; in another, neutrophils were the dominant cellular reaction and necrotic lesions became a prominent feature; and in still another situation, histologic tubercles appeared in one phase of the reaction and no necrotic lesions occurred. As all of these phenomena occurred in the same host during a first infection, it would seem illogical to attribute the variety of cellular responses to an allergic state which is not demonstrable before a few weeks have elapsed.

Perhaps the most significant finding in the experimental studies was the morphologic changes in reinfection. The animals used for these experiments were reactors to tuberculin at the time of reinfection. The predominant pathologic feature in the lungs at the time of death from a first infection with the organism which was used for reinfection was necrotic (caseous) lesions. There occurred a much more prompt and voluminous cellular reaction in the lungs in the reinfection than was found in the first infection. However, moderately large necrotic lesions failed to develop and, after a few months, all of the lesions resolved except those in the superior and posterior portion of the lung. These latter lesions after several months showed necrosis, liquefaction, and sloughing, with the formation of much larger lesions. These also underwent necrosis with eventual liquefaction, sloughing, and cavity formation. Since, in this series of experiments, allergy was already present, it would seem that the changed reaction concerned primarily the phenomenon of resistance which was acquired from a previous infection which had been completely eradicated. It would appear that the interesting phenomenon of hypersensitivity to tuberculin is of relatively little significance.

The writer has long believed that an interpretation of morphologic features in tuberculosis on the basis of the presence or absence of a state of hypersensitivity to tuberculin is open to serious question, and the reasons for this belief have been noted above. The existence of a state of hypersensitivity is a fact. The factors which induce this condition and its real significance remain obscure. In

the opinion of the writer, hypersensitivity to tuberculin has little to do with the demonstrable morphologic features of the disease. This opinion is held despite the fact that a marked inflammatory reaction to the introduction of tuberculin can be induced in an allergic host and no reaction is obtained in a nonallergic host. The difference here may well be due to specific chemical combinations which, in the allergic host, injure tissue in a manner that requires a prompt nonspecific inflammatory cellular response to repair the local damage. Perhaps it may have no other significance.

Undoubtedly a wide range of chemical changes occur during the course of all infections. It is probable that some of these reactions are specific for the infectious agent and some are nonspecific. It would seem hazardous, however, to attempt to differentiate between the specific and nonspecific chemical alterations on the basis of the nature of the cellular inflammatory reaction which follows. This attitude is taken for the reason that the leukocytic types which may participate in the response to the chemical damage are of a limited variety. Moreover, these same leukocytic types respond to a variety of tissue alterations which are in no way related to an infectious process.

The factors concerned with natural and acquired resistance or with immunity to tuberculosis are most obscure. They would seem to be outside the field of morphology. There are certain mechanical situations, however, which would seem to explain some happenings in tuberculosis better than the state of immunity or resistance. It appears that the occurrence of necrosis in an area of tuberculous pneumonia is one evidence of resistance since, at least in the experimental animal, lysis of large numbers of tubercle bacilli occurs along with this phenomenon. The mechanical set-up which is produced by the development of the necrotic lesion in the lung parenchyma can hardly be attributed to a lack of resistance. As it is also a common occurrence to rid the living tissues of necrotic areas by the process of liquefaction and sloughing, this phenomenon can hardly be attributed to a lack of resistance. When this phenomenon occurs in the lung, however, the mechanical features are such that any tubercle bacilli which have survived and multiplied after the process of necrosis are scattered indiscriminately to new areas of lung parenchyma.

It appears that those persons who have a tendency to liquefy and slough necrotic tissue promptly fare much worse than those who lack this tendency. Perhaps this may explain a difference which has been noted between races. Sloughing of a necrotic cervical tuberculous lymph node through the skin is generally followed by complete healing. Sloughing of a necrotic parenchymal lesion in the lung is generally followed by a greater amount of disease. In both instances an attempt is being made to rid the body of noxious necrotic tissue. The difference in end results lies in the different location of the necrotic tissue.

Perhaps the best evidence of increased resistance in progressive pulmonary tuberculosis is the person who is able to survive the expectoration of considerable areas of his lungs. In pulmonary tuberculosis it would seem best to consider first the mechanical factors involved rather than to attribute the situation to a lack of resistance, either inherited or acquired.

It seems probable that persons afflicted with tuberculosis develop as great re-

sistance to the infection as do persons who become infected with other bacteria. The difference in the outcome of the infections would seem to rest to a large extent on the nature of the pathologic processes which are brought into play.

HEMATOGENOUS AND LYMPHOGENOUS DISSEMINATION

The more thoroughly tuberculous infection of the lung is understood, the more evident it becomes that, with infrequent exceptions, tuberculous infection of other organs requires a previous infection of the lung. The morphologic features in other organs closely resemble those found in the lung, if due consideration is given to differences in organ structure and function. It is evident that the tubercle bacillus finds a much more favorable environment for its survival and propagation in some organs than in others.

From the evidence presented from necropsy studies on the cases of sudden and unexpected death, it seems that the initial parenchymal pulmonary focus is the most common source from which an original hematogenous dissemination occurs. Evidence of a hematogenous seeding was unusual in persons who had completely healed a minute primary pulmonary lesion. These persons, although they had been infected, never developed progressive or clinical disease. However, they represent a high proportion of people who do become infected with tubercle bacilli. From this it would appear that, in general, tuberculous infection should not be regarded as a generalized infection. With a progressive primary pulmonary infection, a generalized hematogenous dissemination is found more often than with a progressive reinfection; but again the disease should not be considered to be a generalized infection.

The evidence indicates that some hematogenous seedings may result in few visceral lesions. These commonly heal completely although on occasion a progressive visceral tuberculosis may develop, i.e., bone, joint, kidney, brain. With heavier hematogenous seedings, multiple organs may show a progressive disease. An overwhelming generalized miliary tuberculosis and tuberculous meningitis may result from a heavy seeding of the blood stream with a probable bacteremia. In the writer's experience, these are the only cases in which tubercle bacilli can be demonstrated by culture and animal inoculation of blood.

The original or initial primary pulmonary parenchymal lesion is also the source from which a dissemination by lymphatics occurs. Here it would seem that the bacilli gain entrance to the lymphatics by migrating leukocytes which have phagocytosed tubercle bacilli. The lymphatic dissemination commonly stops in the regional lymph nodes, which act as a screening apparatus for the area or areas of lung affected. The frequency of this phenomenon is attested to by the infrequency of proved exceptions, either to the law of Parrot or to an absence of the primary complex of Ghon.

The evidence from necropsy studies, already referred to, strongly indicates that it is unusual for a further dissemination of the infection to occur by way of the lymphatic system. On occasion, tuberculous infection may progress from one lymph node to another of the respiratory system. Even less often does a blood-borne dissemination occur which has originated from the spilling of bacilli

through large lymph vessels into the blood stream. In the experience of the writer this situation gives rise to a generalized hematogenous dissemination.

It has been impossible to obtain any evidence which would support the thesis that lympho-hematogenous disseminations cause pulmonary parenchymal disease to the exclusion of lesions elsewhere in the body. Neither has the writer obtained any evidence to support the hypothesis that, when lympho-hematogenous seedings do occur, they are restricted to the apical portions of the lungs.

EFFECT OF CHEMOTHERAPY

The effect of chemotherapy upon the morphologic aspects of tuberculosis can be stated simply. From the changes in roentgenographic shadows and from the study of resected specimens, it is evident that the non-necrotic component of the tuberculous disease vanishes in most instances if an efficient chemotherapeutic regimen is in force for at least four months. This would seem to be the portion of the disease which "cleared" in the days before chemotherapy. However, it seems that chemotherapy induces a more rapid disappearance than was observed previously. It is remarkable how great a portion of the disease in some cases may be in a pre-necrotic state at the time chemotherapy is instituted. It may be that chemotherapy can prevent the occurrence of further necrosis if instituted before necrosis has occurred; but there is no morphologic proof to substantiate this assumption. However, in every clinical case there is present a variable necrotic component at the time the disease is discovered. By the use of chemotherapeutic agents, it usually is possible to determine in less time the magnitude of the necrotic component than in the pre-chemotherapy era. The considerable difference between cases is shown in Plates XLII, XLIII, and XLIV.

The common finding of parenchymal scars in resected specimens would seem to indicate that, once histologic tubercles have begun to heal by scar formation, this process cannot be abolished. It may be, however, that tubercles in the early stages may be induced to resolve before scar formation is begun. Again there is no morphologic proof of this.

There is no morphologic evidence that chemotherapy significantly affects a necrotic lesion once it is formed. There is abundant clinical evidence that the majority of patients under chemotherapy have a marked decrease of sputum with disappearance of bacilli in the sputum. Also, in a considerable proportion of cases open cavities disappear roentgenographically. However, similar phenomena occurred prior to the introduction of chemotherapy although the promptness and frequency of occurrence appears to have been less dramatic. It has been found impossible to distinguish between necrotic lesions and filled-in cavities in patients who have had no chemotherapy and in those who have had prolonged chemotherapy. Open cavities tend to contain less exudate although this is not always the case. The morphologic appearance of open-cavity walls is not essentially different in the chemotherapeutically treated and the nontreated cases.

The most disturbing observation in the study of resected specimens is the evidence of continuing liquefaction of some necrotic lesions even after a prolonged and uninterrupted course of chemotherapy. The prevalence of the proc-

ess of liquefaction varied greatly from case to case. It may well be that this process alone will be the factor which will determine the occurrence of relapses of the disease after chemotherapy is stopped. It is the opinion of the writer that the threat of the necrotic lesion has not been overcome by chemotherapy. This pertains to both the necrotic parenchymal and the necrotic endobronchial lesion.

GENERAL COMMENT

The most serious morphologic features of tuberculosis can be briefly and simply stated. The major problem concerns infection of the lung in most instances, tuberculosis of other organs being of secondary importance. In order to produce progressive pulmonary disease, an air-borne particle which contains tubercle bacilli must lodge in a "vulnerable" portion of the lung. These "vulnerable" areas consist of the superior and posterior portions of pulmonary lobes. To cause progressive disease, the initial minute area of open lobular pneumonia must undergo necrosis and liquefaction and slough into a bronchus. This process induces the formation of larger areas of lobular pneumonia which, if they undergo necrosis, may also liquefy and slough. The extent of involvement of lung in the end depends upon the amount of the sloughing debris which is dispersed through the bronchi to the pulmonary tissue. The serious feature of progressive pulmonary tuberculosis is a necrosing, liquefying, and sloughing pathologic process. It is this phase of the pathologic process which causes pulmonary tuberculosis to be a chronic disease with a considerable tendency to relapse.

The seriousness of the pulmonary disease depends upon the quantity of tubercle bacilli in the sloughing material which is dispersed through bronchi to previously uninvolved lung parenchyma. The quantity of bacilli would seem to depend upon the number of bacilli which have been able to survive the process of necrosis and upon the extent to which the surviving bacilli have been able to reproduce after necrosis has occurred.

PLATES XLII–XLIV follow

PLATES XLII, XLIII, AND XLIV

The following plates illustrate a striking contrast in 2 cases in the amount of clearing of roentgenographic shadows during prolonged multiple-drug therapy.

The first case is that of a male Negro twenty-seven years of age. Multiple-drug therapy was used for two years, and extensive clearing of roentgenographic shadows occurred. The chest roentgenograms shown on Plate XLII show the extent of shadows (figure 130) in the left lung at the time of discovery of disease and also the situation just prior to surgery (figure 131). At the time of surgery, repeated cultures of sputum had occasionally yielded a single colony or a few colonies of tubercle bacilli.

Plate XLIV (figure 134) on the left side shows a section of the excised upper lobe reduced one-half. Note the open cavity in the central upper portion. Directly below the cavity are blood vessels and bronchi on cross-section. The small, widely scattered grayish to yellowish-gray foci are small necrotic lesions. Only a few small, widely scattered parenchymal scars were found in the remainder of the lobe. From this it seems apparent that considerable areas of non-necrotic tuberculous pneumonia have resolved. On the other hand, the necrotic remnants persist although chemotherapy was of long duration. Some of the small necrotic lesions, as well as the open cavity, showed that active liquefaction of the necrotic tissue was still in process.

Plate XLIV (figure 135) (× 2) shows the cavity and surrounding lung parenchyma.

The second case is that of a white male, twenty-seven years of age. Multiple-drug therapy had been used for one year prior to surgery, and the sputum became negative for tubercle bacilli on microscopy and culture five months prior to surgery. Chest roentgenograms shown on Plate XLIII show the extent and character of pulmonary shadows in the right upper lobe at the time of diagnosis (figure 132) and just prior to surgery (figure 133). Plate XLIV (figure 134) on the right side shows a cross-section of the lobe reduced one-half. Note the numerous fairly large necrotic lesions. The illustration is representative of the condition found throughout the lobe. There were numerous parenchymal scars, some of moderately large proportions. These were interpreted as organized areas of non-necrotic tuberculous pneumonia. It seems probable that some resolution of disease also had occurred.

Plate XLIV (figure 136) (× 2) shows a recent lobular pneumonic lesion and a sloughing necrotic lesion in the lower half. The blue color in this area is due to the viable cellular inflammatory reaction which in most areas is composed predominantly of neutrophils. This recent lesion indicates that new areas of disease do occur during chemotherapy. The writer has found this to be true in several other specimens. Several other tuberculous lesions are also present in the illustration. In other areas of the lobe there was no evidence of active liquefaction of moderately large necrotic lesions. The reason for the difference in behavior of the necrotic lesions is a major and unexplained phenomenon.

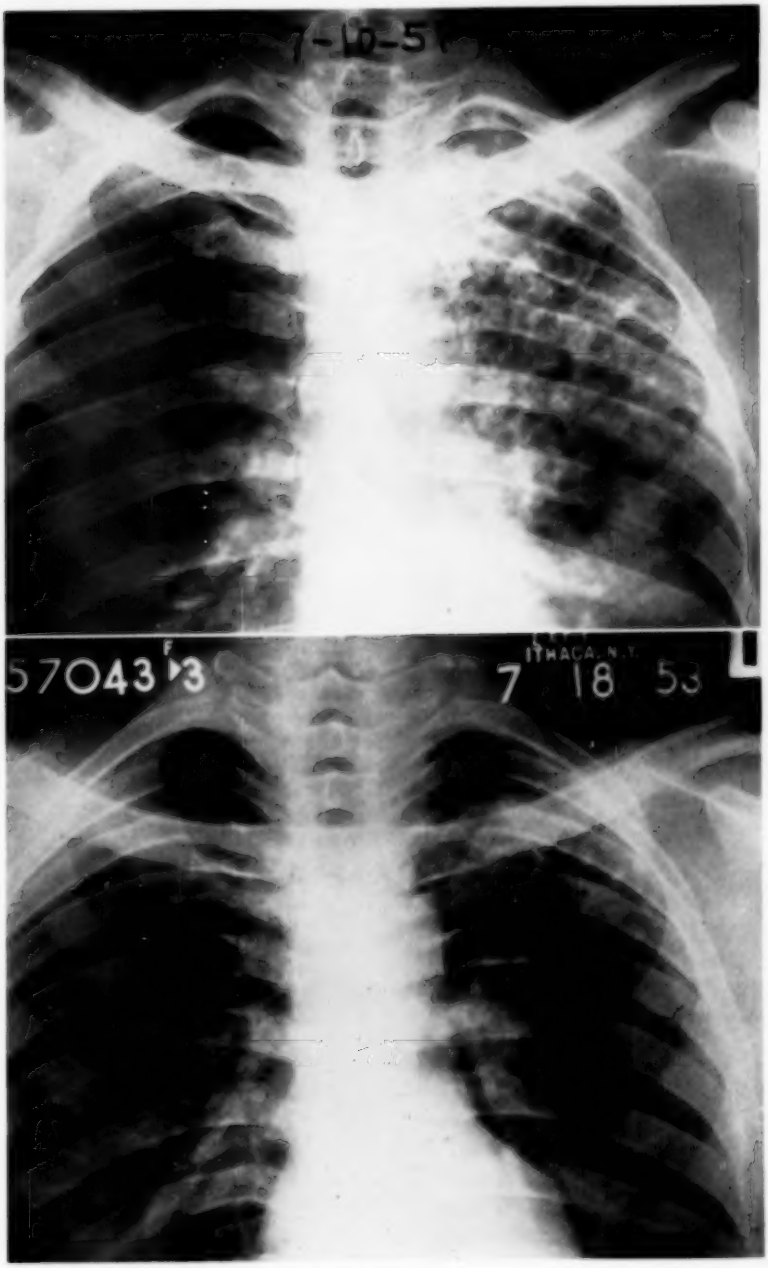


Fig. 130

Fig. 131

PLATE XLII

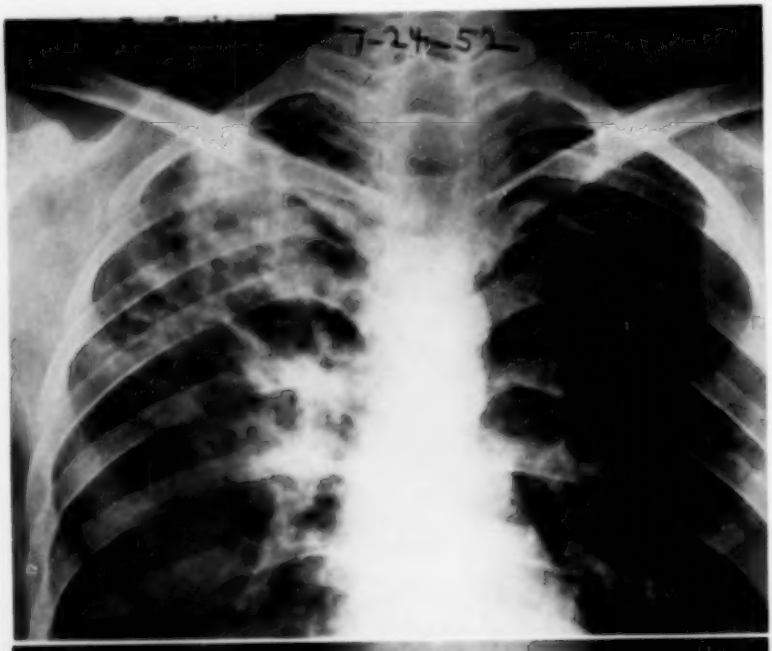


FIG. 132

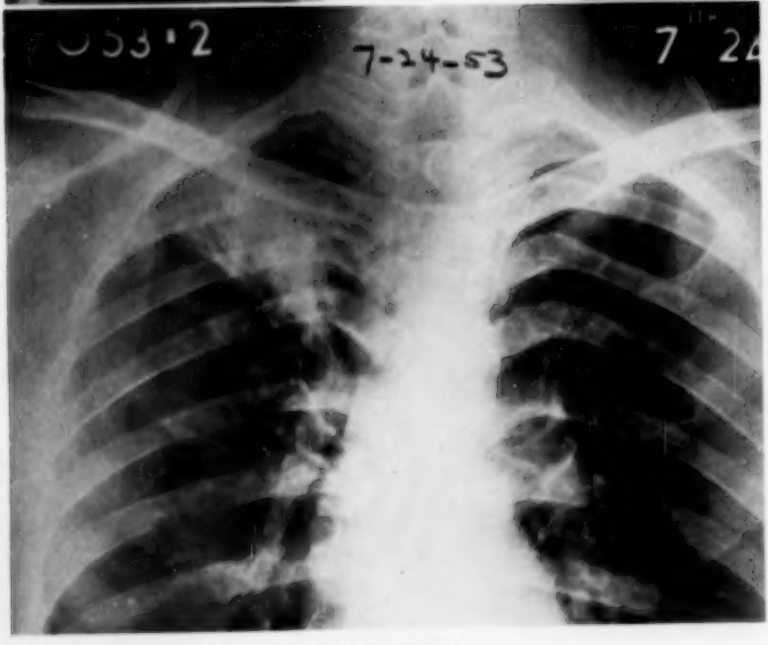


FIG. 133

PLATE XLIII

Fig. 134

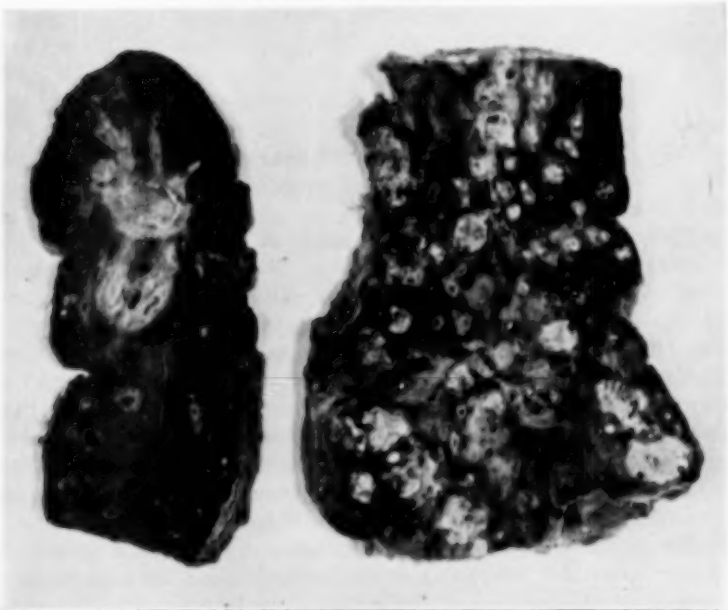
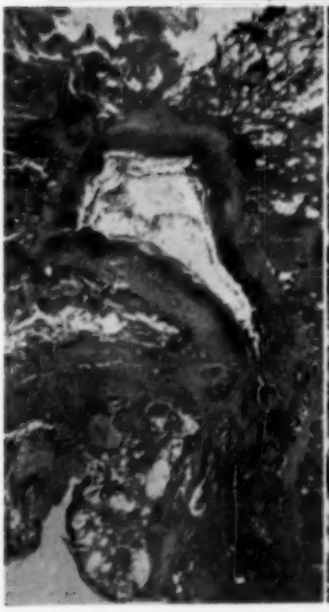


Fig. 135



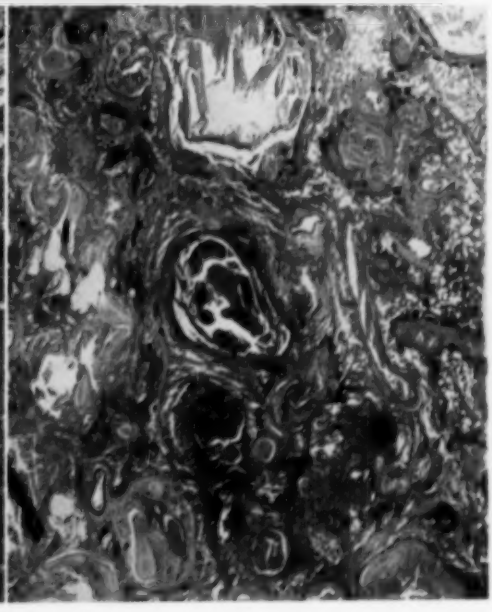


Fig. 136

PLATE XLIV

CHAPTER XI

POSTSCRIPT

The foregoing presentation of the various studies is concluded with a sense of dissatisfaction. Despite the progress that has been made toward an understanding of a complicated pathologic process, questions remain unanswered which are fundamental to a complete knowledge of the dynamics of tuberculous disease. Long observation has convinced the writer that bed rest, collapse of the lung, and chemotherapy, wisely used, all are good "delaying actions." These help to reduce the mortality rate and to restore the majority of tuberculous patients to a state of health that is not infrequently maintained by a restriction of physical activities. Nevertheless, the pathologic evidence is overwhelming that the disease commonly remains in a suppressed unhealed state even in persons who present the picture of health.

Throughout these studies the writer has sought to obtain a comprehensive understanding of the problem of tuberculosis. This has led to a rather close examination of the thinking of the clinician, the surgeon, the epidemiologist, and the public health officer which forms the body of ideas for the various programs aimed at control of the disease. This may seem to be an unorthodox pursuit for a pathologist. Nevertheless, it is believed that the function of a pathologist should extend beyond the development of a nicety and precision of laboratory techniques and the rendering of an accurate diagnosis on a specimen. He should attempt to translate what he observes into terms which will enable those who care for the sick and those who formulate public health programs to understand the dynamics of disease processes with which they have to deal. Furthermore, his investigative endeavors should be directed, in part at least, to the study of pathologic problems suggested by other fields of inquiry.

Controversy concerning the problem of tuberculosis is much livelier today than it was twenty-five years ago. This is a most healthy state of affairs since it clearly indicates that the problem has not been solved; otherwise, there would have occurred a meeting of the minds. It will be fortunate indeed if this controversy leads to the acquisition of new knowledge and to the formulation of sounder concepts.

In the past quarter of a century six major events have occurred which have had a profound impact on the thinking about the problem of tuberculosis. These are:

(*1*) The program of public education. (*2*) The impressive decline in the death rate from the disease. (*3*) The introduction of prophylactic vaccination. (*4*) The advent of promising chemotherapy. (*5*) The greatly renewed interest in the life processes of the tubercle bacillus. (*6*) The use of surgery either to collapse the lung or to resect the area of pulmonary disease.

I would like to consider briefly the way in which basic pathologic facts may be related to each of these rather disjointed events.

No one will dispute the need for education, even continuing education, concerning tuberculosis. One may question, however, where such education should begin and what sort of an educational program should be pursued. The writer has had the interesting experience of witnessing the reaction of three medical students to the contents of Chapter I of the present monograph. Each of these students had taken his course in pathology in prominent medical schools since 1949. Each expressed surprise that there should be any question of the validity of the basic concepts of the disease which had been taught in 1925 and which are still being taught. This suggests that during the past two decades considerable progress has been made toward an understanding of the pathogenesis of pulmonary tuberculosis, and it is unfortunate if the oncoming members of the medical profession are not being made aware of the newly acquired knowledge.

It is recognized that many pathologists are interested in tuberculosis only from a diagnostic standpoint and prefer not to do necropsies on tuberculous subjects. Directors of departments of pathology have frankly stated that, since all of the pathologic facts about tuberculosis were already known, the writer was wasting his time in studying the disease. Professors of pathology have been heard to state that there is nothing of less interest than a tuberculous cavity of a lung. Surely such attitudes would not be voiced were pathologists more conversant with the clinical and socio-economic problems in tuberculosis.

It seems to the writer that a better control of tuberculosis would be possible if the dynamics of the pathologic process were properly presented to medical students who, after all, are to become the practising physicians of tomorrow. This assertion is made because, in most instances, the first responsible person to have an opportunity to recognize a case of tuberculosis is the practising physician. It is at this time that the fate of many tuberculous patients is determined.

Perhaps one should go across the hall to the department of public health and hygiene and suggest that the teaching of the epidemiology of tuberculosis would not suffer from an inclusion of basic information about the pathogenesis of the disease. It is an interesting exercise to show, by graphs, how steadily the mortality rate from tuberculosis has declined during the past fifty years. From such demonstrations one can easily be led to the conclusion that soon tuberculosis no longer will be a problem; a situation which could come to pass if it were true that the mortality rate indicated the major hazard. Unfortunately, this is not so. The major problem revolves about the surviving tuberculous persons who harbor smoldering unhealed disease that only too often flares into activity.

Another aspect of this situation is the not uncommon presence of a tuberculous person who has had stationary pulmonary shadows for many years and who, if thoroughly investigated bacteriologically, would be found to be shedding tubercle bacilli. Patients with disease of this nature can properly be considered as chronic carriers. It is probable that they are the source, often unrecognized, from which a continuing annual crop of new patients acquire the disease.

It is of much greater importance to obtain accurate and reliable data on

morbidity and relapse rates than to reiterate year after year that the mortality from tuberculosis is declining. In this way the major problems in tuberculosis can be given due consideration. From his many visits to the residencies of the tubercle bacillus, the writer has come to appreciate that the future of this parasite is served best by a host who does not die and who remains sufficiently healthy so that the services of a physician are not sought. Or, if a physician is consulted, the situation is probed no further than to make a diagnosis of "chronic bronchitis," "cigarette cough," or "a touch of the asthma."

Another aspect of the problem deserves comment. During the past decade there has been an increasing appreciation that deaths from tuberculosis now are most numerous among white males more than forty years of age. To explain this phenomenon, it has been proposed that these males are a vestige of the exceedingly high incidence of tuberculous infection which is commonly supposed to have existed thirty to forty years ago. On this basis it is argued that tuberculosis is on its way out. Reasoning of this nature has come to be accepted because there is no large volume of statistics to indicate that there is such a condition as reinfection tuberculosis, that is, a new progressive infection in a person who had completely healed a previous infection. There is a certain amount of roentgenographic evidence that some persons develop progressive disease after middle life. However, such evidence has commonly been used to support the allegation that the disease had been dormant for many years—probably since childhood.

In the writer's necropsy studies, an attempt was made to find evidence for and against this concept. Little evidence was found in support of this concept and there was considerable evidence against it. Necropsies on persons more than forty years old who died from pulmonary tuberculosis could be separated into two groups. In one group the presence of old scars, of calcified foci, and of old necrotic lesions clearly indicated that a chronic disease of many years' duration was present. In this group, the condition found in lymph nodes associated with either the pulmonary or the gastrointestinal system suggested that the pulmonary disease was either a chronic progressive primary or a chronic progressive reinfection disease; more often the former than the latter. In the other group, no evidence was found that the disease had been of many years' duration. It was observed on several occasions that the only significant difference between the tuberculous lungs from older persons and those from persons who died in their twenties was that there was considerably more anthracotic pigment in the aging lungs. There appeared to be a preponderance of reinfection tuberculosis in this second group of older persons.

In necropsies in general so little attention has been given to a separation of pulmonary tuberculosis into progressive primary and progressive reinfection disease that there is an insufficient volume of reliable data to make possible a statistical evaluation of the incidence of reinfection disease in persons more than forty years old. Nevertheless, the writer is convinced that progressive reinfection pulmonary tuberculosis is a reality and that tuberculosis can be acquired at any age. There is no justification for complacency with regard to tuberculosis

in older persons and, in the writer's opinion, it is erroneous to consider tuberculosis in this age group as a common vestige from previous decades.

Tuberculin surveys have become an accepted part of the program of public education and the writer is in full accord with the purpose of this procedure. It has shown clearly that only a small percentage develop progressive pulmonary tuberculosis among those who become reactors to tuberculin. The data discussed in the chapter on necropsy studies indicate the reason for this phenomenon. A pathologic lesion, that is, disease, commonly develops, but progressive disease infrequently ensues because of the location of the lesion. The evidence submitted in the chapter on "minimal" pulmonary tuberculosis indicates that considerable delay may occur between the time an individual becomes a reactor to tuberculin and the time progressive disease is found. From this it would seem that the incubation period, the lapse of time between the acquiring of the infection and the clinical manifestation of that infection, would be most unpredictable in tuberculosis. It is suggested that this situation is related to difference of behavior in different persons of the minute *initial* lesion which is too small to be visualized in a chest roentgenogram.

Another feature of the educational program is the emphasis which is given to chest roentgenograms for individuals and for entire communities. The writer is in accord with the purpose of this program. There are, however, some pitfalls in the program which need emphasis. Seldom does a community roentgenographic survey include more than 80 per cent of the residents. This leaves a fairly large segment in which spreaders of the disease may remain undetected. It is well known that not infrequently persons with "chest trouble" avoid having a roentgenogram taken of their chest. Furthermore, the program fails to take into account the problem of reinfection tuberculosis and also the unpredictability in the subsequent behavior of the disease which, from roentgenographic appearance, seems to be of no "clinical" significance. The writer has personally seen several instances of the latter condition in which the person died from extensive disease several years later. These instances have all been in older persons and in males. In these days innocuous-appearing pulmonary shadows in younger adults usually are given careful scrutiny.

It cannot be emphasized too strongly that a single roentgenographic survey of a community cannot predict the future problem of tuberculosis in the community any more than a single chest roentgenogram of an individual can guarantee the future possibility of serious pulmonary tuberculosis in that person. These problems are related inherently to the dynamics of the disease.

Pulmonary tuberculosis is an endemic disease and, since it is air-borne, it can be considered as a herd disease, that is, the tubercle bacillus must gain entrance to the pulmonary tissue of a considerable number of persons in order that a small percentage may develop a progression of the disease. This is clearly shown in the necropsy studies of cases of sudden and unexpected death in which only 20 per cent of those who evidenced infection showed that the disease had progressed to some extent. Of these only one-fourth showed open cavity formation, the most favorable situation for the contamination of the air through coughing. A some-

what similar situation was found in the general necropsy records of large general hospitals. Most of these cases were in males more than forty years of age and were unrecognized clinically. In the writer's opinion, this endemic disease will persist, even if the mortality rate becomes negligible, unless some way is found to detect and to segregate this minute percentage of the population. Moreover, this is the feature of the problem in which reinfection tuberculosis in persons beyond middle age becomes a major issue.

Only those who are intimately engaged in the care of tuberculous patients have a keen appreciation of the socio-economic problem that the disease creates. Recently a newspaper from a city in Upstate New York announced that not a single death from tuberculosis had occurred in the county during the previous year. In the same news item it was also stated that there were more known living tuberculous patients than there were ten years previously. During the previous year, 19 new cases of the disease were reported, whereas in the five years before that there had been an annual average of 23 cases. This situation rightly de-emphasizes the mortality rate from the disease and brings into prominence the socio-economic problem.

On the social side, the problem is one of wrecked lives and broken homes. To a considerable degree this problem revolves about an unreasoning fear of the disease. This is well illustrated by a question recently asked by a tuberculous patient, i.e., whether tuberculous people should develop a "complex" about their disease. When asked what he meant he replied that it seemed best not to talk about the subject among his friends.

The economic phase of the problem manifests itself in several ways. Many tuberculous persons are unable to compete successfully on a job with healthy persons. Employment is denied either because of a social fear or because of a possible liability for monetary compensation. Public health laws forbid a person with sputum positive for tubercle bacilli to work, especially in several categories of employment. The disease has been made compensable in some states, with the employer held responsible for the compensation. This has had an unfortunate effect in one respect. It has caused many hospitals to refuse to have any recognized tuberculous cases among their patients, and in this way makes impossible instruction to medical and nursing personnel with regard to tuberculosis. The writer is familiar with one instance in which this situation has deprived the department of pathology of sufficient material to teach medical students. Millions of dollars still are spent to find new cases and to rehabilitate the known cases, and there appears to be no end in sight to the expenditure of such sums of money. A thoughtful consideration of the many ramifications of the economic problem certainly should cause one to be most dissatisfied with the limited progress that has been made in the solution of the problem of tuberculosis.

Perhaps there has never been a more spectacular attempt to eradicate tuberculosis than has been undertaken during the past decade by prophylactic vaccination with BCG. For a number of years, extensive animal experiments on BCG vaccination were carried out under the writer's direction at the Hegeman Memorial Laboratory at Mt. McGregor, New York. From this experience it

can be stated without reservation that, while such prophylactic vaccination confers a degree of protection, this protection falls short of being completely effective.

In the world-wide program of prophylactic vaccination, two fundamental pathologic facts have not been given due consideration. The first is that a natural primary infection with virulent tubercle bacilli fails to prevent reinfection of the lungs. It would seem unlikely that a tubercle bacillus which has largely lost its pathogenic properties would confer a degree of immunity higher than that which follows infection by fully pathogenic bacilli.

The second fact is that progressive pulmonary tuberculosis rarely develops unless the bacilli happen, by chance, to lodge in a "vulnerable" spot in the lung. This pertains both to primary and to reinfection disease. Because of the peculiar nature of the pathology, it is doubtful that any sort of vaccination can eliminate the problem of pulmonary tuberculosis. On the other hand, animal experimentation suggests that prophylactic vaccination well may lessen the occurrence of the generalized disease which is more frequently encountered in a progressive primary infection than in a progressive reinfection.

Now that the pangs of birth of the chemotherapeutic era are over, it would seem appropriate to scrutinize the lusty infant in a spirit of constructive criticism. A quarter of a century ago the word "cured" was used frequently in the assessment of the end result of sanatorium treatment. A decade ago the word "arrested" had replaced the word "cured." This change in the use of words reflected wisdom gained from experience. Now, with chemotherapy, the word "cured" has again come into use, and the writer questions the wisdom of this change in terminology. In his opinion there have been some unwarranted and too optimistic assumptions relative to chemotherapy in tuberculosis and, unfortunately, a rash of ill-advised publicity has occurred with regard to "miracle" drugs. No one need question the beneficial effects of chemotherapy during its administration, and yet one may seriously question the long-range effect on the "curing" of the disease. It is suggested that the fundamental pathologic facts have not been given due consideration in this matter.

Unfortunately the guinea pig and the mouse have been used to determine, experimentally, the effectiveness of chemotherapeutic agents in tuberculosis. In these animals the experimentally produced disease is a progressive inflammatory process that ends in death in a matter of several weeks. In the experimental infections in mice and guinea pigs which are customarily employed, the necrotic (caseous) lesion that is a prominent feature in the human disease is not allowed to develop before treatment is started. As a consequence, one finds no residual necrotic lesions in these animals after chemotherapy, whereas such lesions in man persist regardless of the length of time a chemotherapeutic agent is given. It is mainly in lesions of this nature in man that tubercle bacilli are harbored. The guinea pig and the mouse serve admirably for the screening of possible chemotherapeutic agents. However, in the writer's opinion, it is necessary to establish a *chronic* disease in animals in which the necrotic lesion is a prominent feature and then determine how effective chemotherapeutic agents may be in

the "curing" of this disease. Under proper conditions this sort of a disease can be established in the rabbit. The reason for this point of view is that all newly discovered cases of pulmonary tuberculosis in man already have necrotic lesions to a greater or lesser extent.

It appears to the writer that from the outset the chemotherapeutic regimens were devised as if pulmonary tuberculosis was analogous to pneumonic lesions caused by many other bacterial agents. In the beginning the criteria for the selection of patients to be treated required that acute "exudative" disease be present or that acute generalized disease or meningitis be manifest. This practice was obviously necessary when the object was to prove that antimicrobial drugs could affect tuberculosis in humans. Nevertheless, the practice automatically excluded a large proportion of the patients present in tuberculosis hospitals. If chemotherapeutic agents can actually "cure" tuberculosis, there is no valid reason why the "chronic" advanced cases cannot be so affected. This does not mean that normal lungs will be obtained, for parenchymal scarring is usually the residue of healed tuberculosis.

On several occasions the writer heard physicians state that chemotherapeutic agents put out the "fire," but they cannot be expected to remove the charred remnants. These charred remnants referred to roentgenographic shadows that persisted after the "fire" had been put out and supposedly were pulmonary scars. Again this reflects an attitude that tuberculous disease is essentially an acute inflammatory process. From the data presented in the previous chapters it should be evident that a considerable part of the roentgenographic shadows which persist subsequent to chemotherapy is composed of unhealed necrotic lesions, many of which were present before chemotherapy was instituted. It is unfortunate that the chronic phase of the disease, which in most instances precedes the acute clinical manifestations and which commonly persists after a subsidence of these manifestations, has not been given due consideration in the formulation of chemotherapeutic regimens.

The writer has had the time and opportunity to study resected tuberculous pulmonary tissue from more than 500 patients. Among these have been cases of minimal and of advanced disease. With few exceptions the resections have been done during the course of chemotherapy. The chemotherapeutic agents have included streptomycin, viomycin, para-aminosalicylic acid, and isoniazid, mostly administered in one or another multiple-drug regimen. The tissues have been resected at any time from two months to three years after the institution of chemotherapy.

From this study, the writer is convinced that these agents can affect tuberculous disease as penicillin can affect acute pneumococcal pneumonia. However, there is one fundamental difference between these two disease processes; in the pneumococcal infection there is no necrosis of tissue, whereas in tuberculosis the process of necrosis is always present and not infrequently is a dominant feature.

It is recognized that necrosis of tissue does occur in some acute pneumonic infections, i.e., acute abscesses caused by aspiration of infected material, infec-

tion with *Klebsiella pneumoniae*, with streptococci, and with staphylococci. However, in such cases there is a distinct, although subtle, difference in the necrotizing process from that in tuberculosis. In the acute necrotizing infections, abscesses are formed and the necrotic tissue is liquefied and expectorated rather promptly. In tuberculosis the abscess formation commonly is aborted before liquefaction occurs and, as a result, the necrotic lesion, commonly called "caseous," remains intact for an indefinite period. There is no convincing evidence that the necrotic lesion is affected by chemotherapy, and too often evidence of liquefaction of these lesions still persists after a year or more of chemotherapy. It is this feature that separates tuberculosis from practically all other bacterial infections of the lung. It is the unpredictable behavior of the necrotic tuberculous lesions that makes it necessary to use prolonged chemotherapy and that also makes it most difficult to determine the length of time chemotherapeutic agents should be used.

With the inclusion of all sorts of tuberculous cases, a considerable change has occurred in the use of chemotherapeutic agents. At present it would seem that neither the problem of the length of treatment nor the one of the combination of chemotherapeutic agents has been resolved. This brings to better perspective the chronic phase of the disease, which proved to be the stumbling block in the era prior to chemotherapy.

It has been suggested that it might be best to treat persons chemotherapeutically as soon as they become reactors to tuberculin. This could be a good idea, provided one could be sure that a progressive disease was underway. However, as pointed out in the chapter on necropsy studies, the large majority of persons who become infected with the tubercle bacillus completely heal their minute infection without the services of a physician.

The publicity given to "miracle" drugs plus the developing tendency to treat patients at home and on an ambulatory basis are greatly complicating the management of the problem of tuberculosis. One of the effects of this situation is that the census in tuberculosis hospitals is on the decline. Another effect is that outpatient clinics are on the increase. Whether the present trend is wise remains to be proved. The policy to treat tuberculous patients at home and on an ambulatory basis may have a popular appeal and is one way to attack the problem. However, in the opinion of the writer, it will be most unfortunate if the decline in the census of tuberculosis hospitals is used as a lever to close these institutions. The problem of tuberculosis is by no means near solution. Hence, it might be timely to include the fundamental pathologic facts in the future planning with regard to the care of the tuberculous patient.

In the past a feature of great concern was the possibility of relapse of the disease subsequent to a return of clinical well-being of a tuberculous person. If chemotherapy "cures" the disease, there should be no relapses. That relapses do occur subsequent to the withdrawal of chemotherapy is now well recognized. This fact should engender an attitude of caution with regard to the ultimate effect of chemotherapy in this disease.

Chemotherapy also has served another purpose: it has given the pathologist the opportunity to demonstrate certain aspects of the pathology of tuberculosis

through the study of resected pulmonary tissue. From such studies it has become possible to emphasize that there is a wide variation in the relative proportion of the non-necrotic and the necrotic components of the disease and also that there is a considerable variation in the amount of residual parenchymal scarring after healing of the non-necrotic component occurs. Moreover, it has become possible to emphasize that there is a considerable variation in the behavior of necrotic lesions in different patients and even of individual lesions in the same patient. All of these features indicate the lack of uniformity in the pathologic process and suggest that the tuberculous patient be considered on an individual rather than on a group basis. The greatest difficulty is that the crudity of present methods does not permit the behavior of residual necrotic lesions to be determined at the time clinical health has been regained. However, this difficulty is not new. This feature has always made the behavior of pulmonary tuberculosis unpredictable.

Chemotherapy has brought to light unsuspected potentialities of the tubercle bacillus. The ability of this organism to accommodate itself to the presence of all known effective chemotherapeutic agents greatly complicates the management of the tuberculous patient. It is natural that the clinician would burden the laboratory with examinations aimed directly at the clinical problem. Despite sympathy with this practice, the writer is convinced that a solution of the problem requires a probing into much more fundamental questions, the answers to which can have no immediate application to the treatment of sick persons. It would seem to be the duty of the clinician to foster vigorously fundamental research in bacteriology. An essential part of this research should be a study of tubercle bacilli obtained directly from tuberculous lesions of various ages. Such a study might well be undertaken with an attitude of healthy dissatisfaction with accepted bacteriologic procedures.

The writer was an early advocate of performing resection surgery during a course of effective chemotherapy. It is recognized that open chest surgery is always a major surgical procedure and that it is not devoid of some risk to the patient. It is also apparent that surgeons will be required to reorient their concepts of the pathologic problem with which they are dealing.

The writer will list briefly the reasons for favoring surgical resections of residual tuberculous disease.

The evidence from necropsy studies is convincing that progressive tuberculosis is frequently not a generalized infection; that pulmonary lymph node tuberculosis in adults usually is an unimportant feature; and that often the pulmonary disease is limited to a relatively small area of lung tissue. Moreover, the evidence is likewise convincing that resection of the pulmonary disease offers, at this time, the best chance of eradicating the dangerous residual pathology.

Chemotherapy cannot help but alter the nature of the bacterial population. If a relapse should occur after chemotherapy is discontinued, further treatment of the patient will be complicated by the altered bacteriologic problem.

Finally, there is no more effective way to demonstrate the dynamics of the pathologic process than to show clinicians and surgeons the condition, present after many

months of chemotherapy, in tissues removed from tuberculous patients who continue to be a problem. There is also no better way to demonstrate that chest roentgenograms, essential as they are, often do not accurately show either the extent or the nature of the disease process.

One of the problems which has arisen as a result of resectional surgery is the question whether the condition found in some patients warrants a major surgical procedure. In this situation usually the argument revolves about the small number and the small size of the necrotic foci which have been found. It is not possible to take a dogmatic stand on this issue because there is no way of knowing how an individual necrotic lesion, regardless of size, may behave. This is not in any way dodging the issue; rather it is a frank admission of an inability to prognosticate the behavior of necrotic lesions. It is not the *size* but rather the subsequent *behavior* of a necrotic lesion which is the issue. It must constantly be borne in mind that progressive pulmonary tuberculosis is usually initiated by a necrotic lesion which is too small to be recognized roentgenographically. It can be stated as a general proposition that small necrotic lesions, i.e., those two to three millimeters in diameter, have a greater tendency to liquefy and slough if they are located in the superior and posterior portions of pulmonary lobes than do similar lesions in the lower portion of lobes.

In this connection it is not infrequent that more disease is found by the surgeon than was anticipated from roentgenographic findings prior to surgery. Moreover, in some patients the disease is found to be so widely scattered that, from a pulmonary functional standpoint, it would seem best not to attempt excision of all disease.

The great variations in the amount and distribution of residual necrotic disease which may be found at surgery after a considerable course of chemotherapy are features to be expected because of the pathologic nature of the disease. These variables probably represent the most difficult problem in the management of a tuberculous patient. Unavoidably, the decision for or against surgery in any patient is the prerogative of the clinician, and here features other than the actual pathologic process may be the deciding factors. Decisions at operation rest entirely in the hands of the surgeon, who should understand the potentials of the disease under his fingers. In neither of these situations should the pathologist be either expected or permitted to make a final decision, since he is not in a position to accept the responsibility of the care of the patient.

Time alone will demonstrate the effectiveness of open chest surgery in tuberculosis. However, it should be given a thorough, intelligent, and fair trial. In this respect it must be realized that the hazard of acquiring a new infection is a possibility that, as yet, is beyond prediction. Tuberculosis, because of the nature of the pathologic process, remains a disease which requires a long period of post-treatment observation before any method of management can be evaluated.

In closing, the writer wishes to return to a consideration of the unanswered fundamental problems in tuberculosis. These can be stated best by a series of questions. What is the nature of the chemical process that induces necrosis? It

does not seem to be related directly to substances generated by the infectious agent. Why do some necrotic lesions undergo liquefaction and slough fairly promptly, while others do so only after a considerable delay, and still others never do? Again the process does not seem to be related directly to the infectious agent. May it not be possible either to induce a clean and prompt slough of all necrotic debris under controlled conditions or to prevent liquefaction completely? Why are tubercle bacilli able to survive and to multiply, sometimes in tremendous numbers, in tissue which was sacrificed to destroy them? Why, in many instances, have these bacilli lost their ability to grow on culture media now in current use and to produce progressive disease in experimental animals? Are these masses of bacilli dead or have their life processes become so altered that accepted laboratory techniques are inadequate to determine their status? Why are some portions of the lung parenchyma more "vulnerable" than others to the implantation of a few tubercle bacilli? It will be necessary to obtain answers to at least some of these questions before one may talk, with sense, about the eradication of tuberculosis.

Investigations directed toward the solution of these questions belong to the field of fundamental rather than applied research. They cannot be expected to have an immediate application to the care of the tuberculous patient or to the formulation of public health programs. However, the knowledge accumulated through such studies would undoubtedly cause a considerable revision in the present methods of procedure.

All of the questions proposed above are rather closely inter-related and preferably should be considered as a unit. The services of the chemist, bacteriologist, and pathologist will be required in the acutal investigation and, if materials from human sources are to be used, the close cooperation of the clinician and the surgeon will be essential. The investigations should be assured of long-range financial support. In the writer's opinion, they should be carried out either in, or in close association with, a tuberculosis hospital, for it has been his experience that one must live intimately with the problem of tuberculosis to gain an appreciation of the inherent difficulties and complexities it presents and to develop a dogged determination to stick with the problem until its solution is assured.

Without doubt, answers to the questions raised will be most difficult to obtain and asking for a solution may seem to be a large order. It must be admitted, however, that the problem of tuberculosis is still immense and, because of this, one might be inclined to be fatalistic about the disease. The writer does not subscribe at all to this attitude. Rather, here is a challenge to complete a task that already has consumed large amounts of human energy and resources. It would be quite unfortunate if no more than a truce could be negotiated with this microscopic, parasitic, vegetable cell. Under these conditions eternal vigilance would be required lest the uneasy truce be broken.

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